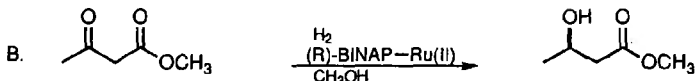


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**ASYMMETRIC HYDROGENATION OF 3-OXO CARBOXYLATES USING
BINAP-RUTHENIUM COMPLEXES: (R)-(-)-METHYL
3-HYDROXYBUTANOATE
(Butanoic acid, 3-hydroxy-, methyl ester, (R)-)**



Submitted by Masato Kitamura, Makoto Tokunaga, Takeshi Ohkuma, and Ryoji Noyori.¹

Checked by Jaechul Shim and Larry E. Overman.

1. Procedure

Caution! BINAP-Ru complexes are rapidly oxidized in solution in the presence of air and all procedures should be carried out under anaerobic conditions using degassed solvents.

A. *[(R)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl]ruthenium(II) complex.* A dry, 80-mL Schlenk tube (Note 1) connected to a supply of argon (Note 2) is equipped with a Teflon-coated magnetic stirring bar and a glass stopper. The flask is charged with $[\text{RuCl}_2(\text{benzene})]_2$ (130.5 mg, 0.261 mmol) (Note 3), (R)-BINAP (341 mg, 0.548 mmol) (Note 4), and then is evacuated and filled with argon. N,N-Dimethylformamide (DMF) (9 mL) (Note 5) is introduced with a hypodermic syringe under a stream of argon and the inlet is sealed by a glass stopper using silicon grease. The suspension is stirred at 100°C for 10 min under argon (Note 6), giving a clear reddish brown

solution (Note 7). The reaction mixture is cooled and concentrated at 1 mm at 50°C with vigorous stirring and then at 0.1 mm for 1 hr to give 500 mg of (R)-BINAP-Ru(II) complex (Note 8) as a reddish brown solid, which is used as the hydrogenation catalyst.

B. (R)-Methyl 3-hydroxybutanoate. A 200-mL, dry Schlenk tube is charged with methyl 3-oxobutanoate (50.0 g, 0.431 mol) (Note 9) and methanol (50 mL) (Note 10) via hypodermic syringes. To this mixture is added the in situ prepared (R)-BINAP-Ru(II) complex (175 mg) (Note 11) under a stream of argon. The resulting yellowish orange solution (Note 12) is further degassed by two freeze-thaw cycles and then transferred by cannula to a dry, argon-filled, 500-mL glass autoclave equipped with a gas inlet tube, a septa-covered stop valve, and pressure gauge (Note 13). The gas inlet tube is attached to a hydrogen source (Note 14) and the air originally present in this tube and the autoclave is replaced by evacuation (to ca. 20 mm) and refilling with hydrogen five times. Hydrogen is introduced into the reaction vessel until the pressure gauge indicates 3 atm. The pressure is carefully released to 1 atm by opening the stop valve. This procedure is repeated three times, and finally hydrogen is pressurized to 4 atm (Note 15). The yellowish orange solution is vigorously stirred at 100°C for 6 hr during which time the hydrogen cylinder is kept connected. After the main valve of the hydrogen cylinder is closed, the reaction mixture is allowed to cool to room temperature, excess hydrogen is carefully bled off, and the apparatus is disassembled. The deep reddish orange contents (Note 16) are placed in a 300-mL, round-bottomed flask, and the glass autoclave is rinsed with three, 20-mL portions of dichloromethane. The solvent is removed by a rotary evaporator, and the residue (Note 17) is distilled to give 47-49 g (92-96% yield) of (R)-(-)-methyl 3-hydroxybutanoate in 97-98% ee as a fraction boiling at 40°C, 2 mm (Note 18).

2. Notes

1. All the apparatus is dried overnight in a 120°C oven before use.
2. Argon gas (99.998%) is purified by passing through the BASF catalyst R3-11 column at 80°C and then through molecular sieves 4Å.
3. $[\text{RuCl}_2(\text{benzene})]_2$, available from Aldrich Chemical Company, Inc., is used without purification.
4. BINAP is 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.²
5. Guaranteed grade DMF, available from Nakarai Chemicals (the checkers used DMF, Certified A.C.S., from Fisher Scientific Company), is distilled over molecular sieves 4Å under argon before use and stored in a 100-mL Schlenk tube. It is degassed by three freeze-thaw cycles.
6. Reaction at a higher temperature for a longer period leads to formation of the ruthenium carbonyl complex $[\text{IR}(\text{KBr})\ 1964\ \text{cm}^{-1}]$. This undesired reaction is suppressed under the present conditions. Use of commercial $[\text{RuCl}_2(1,5\text{-cyclooctadiene})]_n$ or readily available $\text{RuCl}_2[\text{Sb}(\text{C}_6\text{H}_5)_3]_3$ ³ gives similar results on heating in DMF at 160°C for 20 min or in o-dichlorobenzene at 160°C for 10 min. N,N-Dimethylacetamide can be used in place of DMF.
7. The solution is probably a crude mixture of cationic BINAP-Ru(II) complexes such as $[\text{RuCl}(\text{BINAP})(\text{DMF})_3]\text{Cl}$ and $[\text{Ru}(\text{BINAP})(\text{DMF})_4]\text{Cl}_2$. The physical properties are as follows: conductivity 27 Scm^2/mol (DMF); ^{31}P NMR (4:1 DMF- CDCl_3) δ : 60.6 (d, $J = 46$), 61.4 (d, $J = 46$), 61.8 (s). The DMF solution can be used directly for hydrogenation although the reactivity is one-half that of the dried material (Note 8).
8. This complex is probably a mixture of neutral BINAP-Ru(II) complexes such as $\text{RuCl}_2(\text{BINAP})(\text{DMF})_2$ and $[\text{RuCl}_2(\text{BINAP})(\text{DMF})]_n$. The physical properties are as follows: conductivity 0.4 Scm^2/mol (CH_2Cl_2); ^{31}P NMR (CDCl_3) δ : 53.7 (d, $J = 41$), 54.5 (d, $J = 42$), 54.8 (d, $J = 39$), 57.4 (d, $J = 41$), 59.7 (d, $J = 42$), 61.5 (d, $J = 39$).

9. Methyl 3-oxobutanoate, available from Nakarai Chemicals (the checkers used ester purchased from Aldrich Chemical Company, Inc.), is distilled over molecular sieves 4Å under argon and stored in a 200-mL Schlenk tube. It is degassed by three freeze-thaw cycles before use.

10. Guaranteed-grade methanol is dried and degassed at refluxing temperature over magnesium methoxide (from magnesium turnings) under a stream of argon for 6 hr and distilled into a 2-L Schlenk flask. It is further degassed by three freeze-thaw cycles before use.

11. The complex is weighed quickly in the air.

12. The ruthenium complex is moderately soluble in methanol. Suspension in an ultrasonic cleaning bath is employed to achieve complete solution.

13. The glass autoclave is evacuated and filled with argon five times before use. The apparatus is shown in Figure 1. Inside diameter and length are 7 and 14 cm. A Teflon-coated stirring bar of ca. 2 by 4 cm is recommended. The submitters report that vigorous stirring and use of a wide-shaped autoclave (Figure 1) are important in obtaining high yields.

14. Hydrogen of 99.99999% purity (Nippon Sanso) is used. The checkers employed 99.99% grade hydrogen.

15. Satisfactory results are not obtained at atmospheric hydrogen pressure, with slow conversion even at 100°C.

16. The color changes gradually to dark green in the air.

17. Gas chromatographic analysis indicates that the yield of methyl 3-hydroxybutanoate is 98%: column, PEG-20M on Chromosorb WAW (Stainless steel 3 m x 3 φ, Gasukuro Kogyo); column temperature, 120°C; injector temperature, 160°C, carrier nitrogen pressure, 1.2 kg/cm²; *t_R* of methyl 3-oxobutanoate, methyl 3,3-dimethoxybutanoate, and methyl 3-hydroxybutanoate are 31.5, 34.0 and 41.7 min, respectively.

18. The product has the following spectral properties: ^1H NMR (270 MHz, CDCl_3) δ : 1.24 (d, 3, $J = 6.3$, CH_3CHOH), 2.43 (dd, 1, $J = 8.3$ and 16.5, CHH), 2.52 (dd, 1, $J = 4.3$ and 16.5, CHH), 3.01 (br s, 1, OH), 3.72 (s, 3, CH_3O), 4.2-4.3 (m, 1, CHOH); IR (CHCl_3) cm^{-1} : 3450, 2980, 1735, 1440, 1380, 1285, 1180, 1070, 1005; $[\alpha]_{\text{D}}^{25}$ -23.1° to -23.6° (neat) [lit.⁴ $[\alpha]_{\text{D}}^{22}$ -23.5° (neat)].

The enantiomeric excess is determined to be 97-98% by HPLC analysis after converting an aliquot of the product to the (R)- α -methoxy- α -trifluoromethylphenyl-acetate [(R)-MTPA ester]. An aliquot of the crude reaction product (17.5 mg, 148 μmol) is dissolved in dichloromethane (0.5 mL). To this solution are added (S)-MTPACl (75.0 mg, 297 μmol) (Note 19) and pyridine (50 μL) and the mixture is kept at 20°C for 12 hr. To this are added ether (2 mL) and water (1 mL) and the mixture is vigorously stirred for 15 min. The aqueous layer is extracted with two 2-mL portions of ether and the combined organic layers are successively washed with 1 N hydrochloric acid (3 mL), 1 N sodium hydroxide (3 mL), water (3 mL), and brine (3 mL). Drying over anhydrous sodium sulfate, evaporation of the solvent under reduced pressure, and purification by flash chromatography [silica gel (Fuji Davison BW 300), 2 g; eluent, 1:20 and then 1:7 ether-hexane mixture] afford 45 mg (91% yield) of the (R)-MTPA ester. ^1H NMR (270 MHz, CDCl_3) δ : 1.34 (d, 3, $J = 6.3$, CH_3), 2.57 (dd, 1, $J = 4.6$ and 16.2, CHH), 2.74 (dd, 1, $J = 8.6$ and 16.2, CHH), 3.53 (br s, 3, $J = 1.3$, CH_3OCCF_3), 3.67 (s, 3, CH_3OCO), 5.55 (ddq, 1, $J = 4.6$ and 8.6 and 6.3, CHOCO), 7.3-7.6 (m, 5, aromatic). HPLC analysis of this ester [column, YMC 003-3 SIL (250 mm x 4.6 mm) and 002-3 SIL (150 mm x 4.8 mm); eluent, 1:5 ether-hexane mixture] shows two signals with t_{R} of 18.6 and 20.7 min in a 98.9:1.1 ratio assignable to the (R,R)- and (R,S)-diastereomers, indicating 98% ee. The checkers used a SUPELCOIL LC-SI column (250 mm x 4.6 mm); eluent 7:1 hexane-ethyl acetate with RI detection and observed two signals (t_{R} , 13.7 and 15.0 min) with 98.6:1.4 ratio, indicating 97% ee.

19. The (S)-MTPACI is prepared by Mosher's method⁵ from (R)- α -methoxy- α -(trifluoromethyl)phenylacetic acid purchased from Aldrich Chemical Company, Inc.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

Optically pure anti, (R)-3-hydroxybutanoates can be obtained by alcoholysis of poly-(R)-3-hydroxybutanoate, a fermentation product of fructose by *Alcaligenes eutrophus*.⁴ (S)-Ethyl 3-hydroxybutanoate in 84-87% ee can be synthesized in 57-67% yield on a decagram-scale by an *Organic Syntheses* procedure⁶ using bakers' yeast reduction of ethyl 3-oxobutanoate with the aid of sucrose.⁷ In order to obtain enantioselectivity as high as 95-97% ee, the substrate concentration should be kept below 1 g/L.⁸

Among some syntheses of optically active 3-hydroxy carboxylates including optical resolution,⁹ enantioselective aldol reactions between aldehydes and chirally-modified enolates,¹⁰ cinchona alkaloid-catalyzed [2+2] cycloaddition between aldehydes and ketene,¹¹ enantioselective hydride reduction¹² or hydrogenation^{13,14} of 3-oxo carboxylic acid derivatives, the most simple and most desirable would be asymmetric hydrogenation of 3-oxocarboxylates aided by chiral metal catalysts. Methyl 3-oxobutanoate can be hydrogenated by using a homogeneous chiral phosphine rhodium complex¹³ and a heterogeneous Raney nickel catalyst modified

by tartaric acid and sodium bromide,¹⁴ affording methyl 3-hydroxybutanoate in up to 71% ee and 87% ee, respectively.

Hydrogenation of 3-oxobutanoic acid esters catalyzed by $\text{Ru}(\text{OCOCH}_3)_2[(\text{R})\text{-BINAP}]$ ¹⁵ proceeds slowly and in very low optical yield. However, addition of two equivalents of hydrogen chloride to the ruthenium complex facilitates the hydrogenation of methyl 3-oxobutanoate in methanol under the 100-atm, room temperature conditions to give the corresponding (R)-hydroxy ester in 97% isolated yield and in greater than 99% ee. $\text{RuX}_2(\text{BINAP})$ (empirical formula, $\text{X} = \text{Cl}, \text{Br}, \text{or I}$),¹⁶ is prepared by mixing $\text{Ru}(\text{OCOCH}_3)_2(\text{BINAP})$ and hydrogen chloride, hydrogen bromide, hydrogen iodide, or iodotrimethylsilane in a 1:2 mole ratio followed by removal of the solvent. $[\text{RuCl}(\text{benzene})(\text{BINAP})]\text{Cl}$ ¹⁷ or $\text{Ru}_2\text{Cl}_4(\text{BINAP})_2[\text{N}(\text{C}_2\text{H}_5)_3]$ ¹⁸ are also usable as catalyst precursor. The present crude BINAP-Ru(II) complexes prepared by high-temperature ligand exchange¹⁹ possess reactivities and selectivities comparable to these materials. In research laboratories, one may conduct relatively small-scale reactions in a Parr apparatus or an ordinary thickwalled glass vessel equipped with a Young's tap under pressure as low as 4 atm and at 80-100°C.²⁰ Large-scale reactions are performed conveniently under high pressure by using a stainless steel autoclave at room temperature.

The present catalytic, asymmetric hydrogenation using BINAP-Ru(II) complexes is the first practical chemical procedure for the preparation of (R)- or (S)-3-hydroxybutanoates. Characteristic features of this method include high chemical and optical yields, high efficiency of chiral multiplication (a substrate to catalyst mol ratio of >1000), easy access to both antipodes, clean reactions with high (up to 50%) substrate concentrations, and simple isolation of products by distillation. Some examples of the high-pressure, enantioselective hydrogenation of 3-oxo carboxylates using halogen-containing preformed BINAP-Ru(II) complexes are given in the Table.²¹

This method has been used to effect practical asymmetric syntheses of carnitine²² and statine,²³ important, unusual amino acids. Highly stereoselective hydrogenation via dynamic kinetic resolution has been realized with chirally-labile, racemic, 2-substituted 3-oxo carboxylic esters,^{24,25} allowing stereocontrolled synthesis of natural and unnatural threonine, DOPS (anti-Parkinsonian agent), a useful intermediate for the synthesis of compounds such as carbapenems or carbocyclic analogues of prostacyclin. This methodology can be further extended to a variety of functionalized ketones that have directive groups such as dialkylamino, hydroxyl, alkoxyl, siloxyl, keto, alkoxycarbonyl, alkylthiocarbonyl, (dialkylamino)-carbonyl, carboxyl, and halogen.²⁶

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Figure 1. A low-pressure hydrogenation apparatus

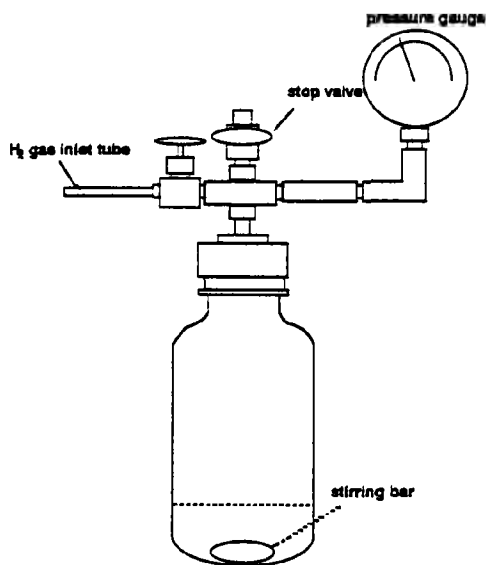
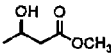
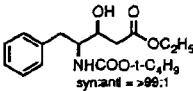
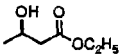
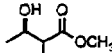
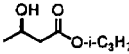
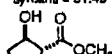
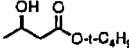
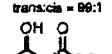
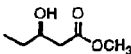
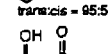
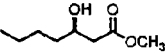
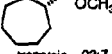
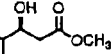
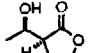
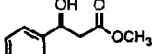
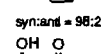
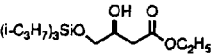
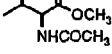
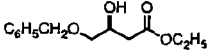
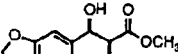
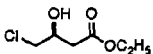
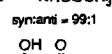
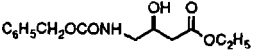
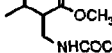
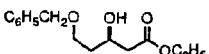
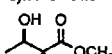


TABLE
OPTICALLY ACTIVE 3-HYDROXY CARBOXYLATES OBTAINED BY (R)-BINAP-Ru-CATALYZED
ASYMMETRIC HYDROGENATION OF 3-OXO CARBOXYLATES^a

Product	%ee	Product	%ee
	>99	 syn:anti = >98:1	99
	99		syn, 97 anti, 98
	98		trans:cis = 86:1
	98		trans:cis = 95:5
	100		trans:cis = 93:7
	98		94
	>99		syn:anti = 98:2
	85		98 ^c
	95		syn:anti = 98:1
	98 ^b		94 ^c
	97 ^b		98 ^c
	88		syn:anti = 94:6
	99		96

^aHydrogenation catalyzed by preformed RuX₂(BINAP) (X = Cl, Br, or I) at room temperature at 100 atm of hydrogen.

^b100°C. ^cIn CH₂Cl₂.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(R)-(-)-Methyl 3-hydroxybutanoate: Butyric acid, 3-hydroxy-, methyl ester, D-(-)-(8);
Butanoic acid, 3-hydroxy- methyl ester, (R)- (9); (3976-69-0)

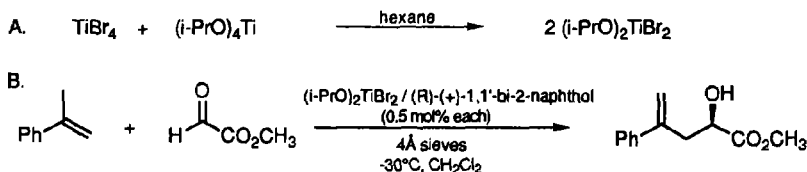
[(R)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl]dichlororuthenium: Ruthenium,
[[1,1'-binaphthalene]-2,2'-diylbis(diphenylphosphine)-P,P']dichloro- (12);
(115245-70-0)

Benzeneruthenium(II) chloride dimer: Ruthenium, bis(η^6 -benzene)di-
 μ -chlorodichlorodi- (9); (37366-09-9)

(R)-BINAP = 2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl: Phosphine,
[1,1'-binaphthalene]-2,2'-diylbis(diphenyl-, (R)- (10); (76189-55-4)

Methyl 3-oxobutanoate: Butanoic acid, 3-oxo-, methyl ester (9); (105-45-3)

**ASYMMETRIC CATALYTIC GLYOXYLATE-ENE REACTION:
METHYL (2R)-2-HYDROXY-4-PHENYL-4-PENTENOATE
(Benzenebutanoic acid, α -hydroxy- γ -methylene, methyl ester, (R)-)**



Submitted by Koichi Mikami, Masahiro Terada, Satoshi Narisawa, and
Takeshi Nakai.¹

Checked by Masami Okabe, Ruen-Chu Sun, and David L. Coffen.

1. Procedure

A. *Diisopropoxytitanium(IV) dibromide* (Note 1). A 50-mL, two-necked, round-bottomed pre-weighed flask equipped with a magnetic stirring bar, a rubber septum, and an argon inlet is charged with 20 mL of hexane (Note 2) and titanium(IV) bromide (7.3 g, 20 mmol) (Note 3). To the red-brown suspension is added titanium(IV) isopropoxide (5.9 mL, 20 mmol) (Note 4) slowly (~ 7 min) at ambient temperature from a syringe. The addition of titanium(IV) isopropoxide causes the mixture to warm to about 37°C. After stirring for 10 min, the now yellow solution is allowed to stand for 6 hr at room temperature, and the pale yellow precipitate that forms is isolated by removing the supernatant liquid with a syringe. The solid residue is then washed with hexane (5 mL x 2) and recrystallized from hexane (10 mL). Recrystallization is carried out in the same flask by heating the solution to reflux and then leaving it at room

temperature overnight. Again the supernatant liquid is removed with a syringe and the crystalline residue is vacuum dried to give 5.7 g (44%) of yellow, *highly moisture sensitive* product. While still in the original flask, this product is dissolved in 88 mL of dry toluene to give a 0.2 M solution (Note 5).

B. Methyl (2*R*)-2-hydroxy-4-phenyl-4-pentenoate. A 100-mL, four-necked, round-bottomed flask equipped with a magnetic stirring bar, thermometer, two dropping funnels, and an argon inlet is charged with 20 mL of methylene chloride (Note 6) and (R)-(+)-1,1'-bi-naphthol (Note 7) (100 mg, 0.35 mmol). The suspension is stirred until the binaphthol is completely dissolved. Powdered molecular sieves 4 Å (2 g) (Note 8) are then added. To the resultant suspension is added a 0.2 M toluene solution of diisopropoxytitanium dibromide (1.75 mL, 0.35 mmol) by syringe at room temperature. After stirring for 1 hr at room temperature, the reaction mixture is cooled to -35°C. To the reaction mixture is added dropwise a mixture of α -methylstyrene (14 mL, 108 mmol) and methylene chloride (5 mL) followed by a solution of freshly distilled methyl glyoxylate (Note 9) (6.16 g, 70.0 mmol) in methylene chloride (20 mL) over 30 min. The mixture is stirred at -35° to -30°C (Note 10) for 6 hr. Progress of the reaction is monitored by thin layer chromatography (Note 11). Even after 6 hr, a small amount of unreacted methyl glyoxylate is detected. The solution is poured into saturated sodium hydrogen carbonate (30 mL). The molecular sieves are removed by filtration through a pad of Celite, and the filtrate is extracted with ethyl acetate (80 mL x 3). The combined organic layers are washed with brine (50 mL x 2). The extract is dried over magnesium sulfate and evaporated under reduced pressure. Fractional distillation gives 12.1 g (84%) of methyl 2-hydroxy-4-phenyl-4-pentenoate (Notes 12 and 13). The enantiomeric purity is 93-95% ee by HPLC analysis using a chiral column (Note 14) or by lanthanide induced shift (LIS) NMR measurement with (+)-Eu(dppm)₃ (Note 15) after conversion to the α -methoxy ester (Note 16).

2. Notes

1. Diisopropoxytitanium(IV) dibromide is prepared following the preparative procedure for diisopropoxytitanium(IV) dichloride.²

2. Hexane is freshly distilled from calcium hydride (CaH_2) or dried over 4 Å molecular sieves.

3. Titanium(IV) bromide is purchased from Aldrich Chemical Company, Inc. This material is very moisture sensitive and is therefore weighed and transferred under an argon blanket.

4. Titanium(IV) isopropoxide is purchased from Tokyo Kasei Co., Ltd. or Aldrich Chemical Company, Inc.

5. Storage of the solution in a refrigerator is recommended.

6. Methylene chloride is freshly distilled from CaH_2 or dried over 4 Å molecular sieves.

7. (R)-(+)-1,1'-Bi-2-naphthol is purchased from Wako Pure Chemical Industries Ltd. or Aldrich Chemical Company, Inc.

8. Molecular sieves 4 Å (activated powder) are purchased from Aldrich Chemical Company, Inc.

9. Methyl glyoxylate can be prepared following a literature procedure.³ The checkers used commercial material supplied by Hoechst Celanese, Specialty Chemicals. Immediately before use, the material is depolymerized by vacuum distillation from phosphorus pentoxide (P_2O_5) (10% weight); bp $62^\circ\text{C}/60\text{ mm}$.

10. In order to achieve high chemical and optical yields, the reaction temperature must be kept in the range of -30 to -35°C .

11. E. Merck silica gel 60 F-254 plates are used, with 2:1 v/v hexane:ethyl acetate as eluent, $R_f = 0.4$ and iodine vapor for visualization.

12. The product has the following spectral and physical characteristics: IR (neat, KBr) cm^{-1} : 3450 (br,s), 2940 (s), 1730(s), 1440 (m), 1030 (m), 910 (m), 780 (s), 710 (s); ^1H NMR (200 MHz, CDCl_3) δ : 2.76 (bs, 1 H, OH), 2.88 (dd, 1 H, $J = 8.1, 13.5$, CCH_2CH), 3.13 (dd, 1 H, $J = 4.5, 13.5$, CCH_2CH), 3.68 (s, 3 H, OCH_3), 4.33 (dd, 1 H, $J = 4.5, 8.1$, CHOH), 5.28 (m, 1 H, $\text{C}=\text{CH}_2$), 5.48 (m, 1 H, $\text{C}=\text{CH}_2$), 7.3-7.5 (m, 5 H, Ar); ^{13}C NMR (50 MHz, CDCl_3) δ : 40.4 (t), 52.2 (q), 69.2 (d), 116.5 (t), 126.6 (d), 127.9 (d), 128.6 (d), 140.4 (s), 143.7 (s), 175.1 (s); $[\alpha]_{\text{D}}^{23} -30.55^\circ$ (CHCl_3 , c 4.83) (for 97% ee R); m/z : Found M^+ 206.0936, $\text{C}_{12}\text{H}_{14}\text{O}_3$ requires M^+ , 206.0943; mp $36-38^\circ\text{C}$.

13. Fractional distillation is carried out as follows: bp $105-106^\circ\text{C}/0.2$ mm; first fraction: 0.7 g, 5% ($< 105^\circ\text{C}$); main fraction: 12.1 g, 84% ($105-106^\circ\text{C}$); last fraction: 0.3 g, 2% ($> 106^\circ\text{C}$).

14. SUMICHIRAL OA-2500I is available from Sumitomo Chemical Co., Ltd. The eluent was hexane/1,2-dichloroethane/ethanol, 200:40:1, with a flow rate of 0.5 mL/min, and detection by 254 nm light. The t_{R} of the (R)-isomer (16.8 min) is shorter than that of the (S)-isomer (18.3 min). The checkers used a CHIRACEL OC column supplied by Daicel Chemical Industries, Ltd., with 10% isopropyl alcohol/heptane as the mobile phase.

15. The shift reagent $\text{Eu}(\text{dppm})_3$ (30 w/v% $\text{CCl}_2\text{FCClF}_2$ solution) is available from Daiichi Kagaku Yakuin Co.⁴

A 10- μL sample of the α -methoxy ester is dissolved in 0.5 mL of CDCl_3 and transferred to an NMR tube. A 5- μL portion of (+)- $\text{Eu}(\text{dppm})_3$ (30 w/v% $\text{CCl}_2\text{FCClF}_2$ solution) is added to the α -methoxy ester sample. The mixture is shaken well, and the ^1H NMR spectrum is recorded. Additional portions of the shift reagent solution are added in 5- μL portions until the methyl ether resonance shifts downfield beyond that of the methyl ester and shows baseline resolution of the methyl ester and methyl ether resonances from the two enantiomers. (Four singlets should be observed). In total 15-20 μL of the shift reagent solution should be required to achieve the desired shift. At

that point, a chemical shift difference of the methyl esters (about 0.1 ppm) should be observed. The % ee is obtained by integration of the two methyl ester peaks. The chemical shifts of the α -methoxy groups of (R)-methoxy esters are lower than those of the (S)-isomers, and in contrast those of the methyl ester groups of (R)-methoxy esters are higher than those of the (S)-isomers.

16. The α -methoxy ester is prepared following a literature procedure:⁵ To a mixture of methyl iodide (0.3 mL) and the ene product (104 mg, 0.50 mmol) in ether (1-2 mL) is added silver(I) oxide (0.23 g). The reaction mixture is stirred for 1 day at room temperature. The suspension is filtered through a pad of Celite and the filtrate is evaporated under reduced pressure. Chromatographic purification of the residue gives the α -methoxy ester in quantitative yield (110 mg).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

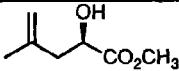
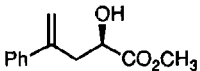
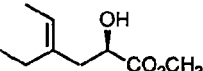
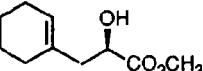
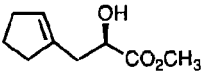
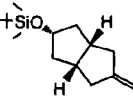
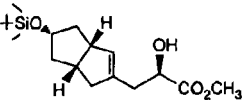
3. Discussion

A full account⁵ describes the enantioselective carbonyl-ene reaction of glyoxylate esters catalyzed by a binaphthol-derived chiral titanium complex that is potentially useful for the asymmetric synthesis of α -hydroxy esters of biological and synthetic importance.⁶ The present procedure is applicable to a variety of 1,1-disubstituted olefins to provide ene products in extremely high enantiomeric purity by the judicious choice of the dichloro or dibromo chiral catalyst (see Table). In certain glyoxylate-ene reactions involving removal of a methyl hydrogen, the dichloro catalyst

is superior to the dibromo catalyst in enantioselectivity, although lower in reactivity (see Table, entries A and B). In reactions involving removal of a methylene hydrogen, the dibromo catalyst is superior in both enantioselectivity and reactivity (see Table, entries C, D, and E); the dibromo catalyst provides a higher % ee, while both catalysts provide equally high (ca. 90%) E selectivity (see Table, entry C). Since both (R)- and (S)-binaphthol are commercially available in optically pure form, the present asymmetric process allows the synthesis of both enantiomers of α -hydroxy esters and their derivatives.

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TABLE
ASYMMETRIC CATALYTIC GLYOXYLATE-ENE REACTIONS WITH 1,1-
DISUBSTITUTED OLEFINS^a

Entry	Olefin	(i-PrO) ₂ TiX ₂ (X)	Catalyst mol%	Time hr	Product	%Yield	%ee ^b		
A		Cl	10	8		72	95	R	
						68	95	S ^c	
		Br	10	3		87	94	R	
B		Cl	1.0	8		97	97	(R)	
		Br	1.0	3		98	95	(R)	
C		Cl	10	8		68 ^d	94 ^e	(R)	
		Br	5	3		73 ^f	98 ^e	(R)	
D		Cl	10	8		82	97	(R)	
		Br	5	3		89	98	(R)	
E		Cl	10	8		93	88	(R)	
		Br	5	3		92	89	(R)	
F		Cl	10	3		77 ^g	99 ^h	(R)	
		Br	10	3		100 ^g	99 ^h	(R)	

^aAll reactions were run on scale of 1 mmol of methyl glyoxylate by the representative procedure described in the text. ^bDetermined as described in Note 14 and/or 15. The configuration in parenthesis could be assigned by the similarity in shift pattern seen in the LIS-NMR spectra using (+)-Eu(dppm)₃ as a chiral shift reagent. ^c(S)-BINOL was used instead of the (R)-counterpart. ^dCombined yield of the (E)- and (Z)-isomer (E/Z = 89 : 11). ^eRefers to the optical purity of the major (E)-product. ^fCombined yield of the (E)- and (Z)-isomer (E/Z = 91 : 9). ^gCombined yield of the diastereomeric mixture (96 : 4). ^hRefers to the optical purity of the major isomer.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Methyl (2R)-2-hydroxy-4-phenyl-4-pentenoate: Benzenebutanoic acid, α -hydroxy- γ -methylene, methyl ester, (R)- (12); (119072-58-1)

Diisopropoxytitanium(IV) dibromide: Titanium, dibromobis(1-methylethoxy)-, (T-4)- (9); (37943-35-4)

Titanium(IV) bromide: Titanium bromide (8,9); (7789-68-6)

Titanium(IV) isopropoxide: Isopropyl alcohol, titanium(4+) salt (8); 2-Propanol, titanium(4+) salt (9); (546-68-9)

(R)-(+)-1,1'-Bi-2-naphthol: [1,1'-Binaphthalene]-2,2'-diol, (R)-(+)- (8);

[1,1'-Binaphthalene]-2,2'-diol, (R)- (9); (18531-94-7)

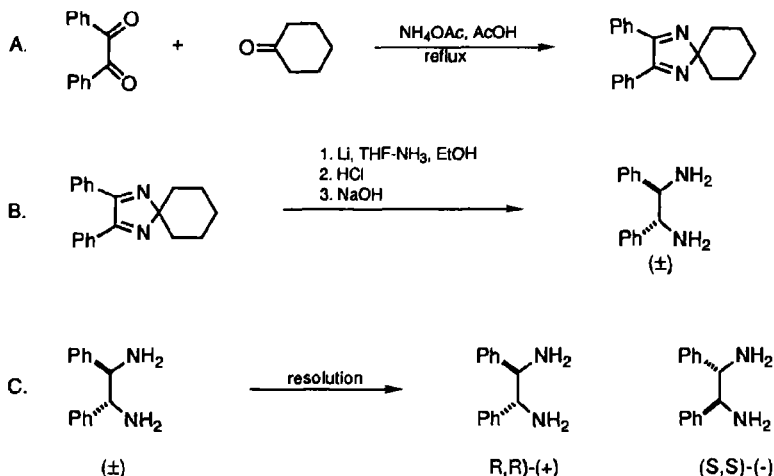
α -Methylstyrene: Styrene, α -methyl- (8); Benzene, (1-methylethenyl)- (9); (98-83-9)

Methyl glyoxylate: Glyoxylic acid, methyl ester (8); Acetic acid, oxo-, methyl ester (9); (922-68-9)

(1R,2R)-(+)- AND (1S,2S)-(-)-

1,2-DIPHENYL-1,2-ETHYLENEDIAMINE

(1,2-Ethanediamine, 1,2-diphenyl-, [R-(R*,R*)]- and [S-(R*,R*)]-)



Submitted by S. Pikul¹ and E. J. Corey.²

Checked by Scott C. Jeffrey and James D. White.

1. Procedure

Caution! Parts A and B of this procedure should be carried out in an efficient hood to avoid exposure to noxious vapors (acetic acid, ammonia).

A. *2,2-Spirocyclohexane-4,5-diphenyl-2H-imidazole* (Note 1). A 2-L, three-necked, round-bottomed flask equipped with a mechanical stirrer and a reflux condenser is charged with 1.0 L of glacial acetic acid (Note 2), 158 g (0.75 mol) of

benzil (Note 2), 400 g of ammonium acetate (Note 2) and 80 mL (0.77 mol) of cyclohexanone (Note 2). The mixture is stirred and heated at reflux temperature for 1.5 hr (Note 3) and then, while hot, poured into 3 L of vigorously stirred water. The mixture is left overnight to cool to ambient temperature, the crystals are collected by filtration, washed 4 times with 300 mL of water, crushed in a mortar and dried under reduced pressure to give 205-210 g (95-97%) of the imidazole as yellowish-green crystals, mp 105-106°C, lit.³ mp 107-108°C (Note 4).

B. (±)-1,2-Diphenyl-1,2-ethylenediamine. A 2-L, four-necked, round-bottomed flask equipped with a mechanical stirrer, thermometer and dry ice condenser is charged with 72.0 g (0.250 mol) of 2,2-spirocyclohexane-4,5-diphenyl-2H-imidazole. The flask is flushed with argon, and 400 mL of tetrahydrofuran (Note 5) is added. The mixture is stirred until all solids dissolve, cooled to -78°C (dry ice/acetone bath) and treated with a stream of gaseous ammonia (Note 6) until the volume of liquid increases by about 400 mL (Note 7). One of the side necks is then equipped with a solids addition funnel and 6.94 g (1.00 mol) of lithium (Note 8) is slowly introduced by cutting the wire with scissors in a gentle stream of argon. The rate of lithium addition is such that the temperature does not rise above -65°C. Following the addition of lithium, the mixture is stirred for 30 min and 30 mL (1.0 mol) of ethanol (Note 9) is slowly added. The mixture is stirred for an additional 20 min and 70 g of ammonium chloride is added. The cooling bath is removed, the mixture is allowed to warm to 0°C, 400 mL of water is carefully introduced, and the phases are separated. The aqueous phase is washed 3 times with 300 mL of ether and the combined organic extracts are washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated with a rotary evaporator to about 200 mL. The solution is transferred to a 1-L, one-necked, round-bottomed flask equipped with a mechanical stirrer, cooled to 0°C and treated with 300 mL of 2 N aqueous hydrochloric acid. The biphasic mixture is vigorously stirred at ambient temperature for 1 hr, 500 mL of water is added and phases are separated.

The organic phase is washed with 150 mL of water and the combined aqueous phases are extracted with 300 mL of dichloromethane. The aqueous solution is then carefully treated with 300 mL of 2 N aqueous sodium hydroxide and the mixture is extracted 4 times with 150 mL of methylene chloride. The combined organic extracts are washed with brine, dried over anhydrous sodium sulfate, and filtered. Removal of volatile material under reduced pressure (water aspirator) gives 47-50 g (89-94%) of racemic diamine as a pale yellow solid, mp 81-82°C, lit.⁴ mp 82°C corr. (Note 10).

C. (1*S*,2*S*)-(-)- and (1*R*,2*R*)-(+)-1,2-Diphenyl-1,2-ethylenediamine (Note 11). A 1-L, round-bottomed flask equipped with a mechanical stirrer is charged with 42.5 g (0.200 mol) of the racemic diamine and 230 mL of ethanol (Note 9). The solids are dissolved by heating the mixture to 70°C whereupon a hot (70°C), homogeneous solution, of 30.0 g (0.200 mol) of (L)-(+)-tartaric acid (Note 12) in 230 mL of ethanol is added (Note 13). The tartrate salts precipitate immediately, and after the mixture is cooled to ambient temperature, the crystals are collected by filtration, washed twice with 60 mL of ethanol, and dried under reduced pressure. The solids are dissolved in 230 mL of boiling water, 230 mL of ethanol is added and the homogeneous solution is allowed to cool slowly to room temperature. The crystals are collected by filtration, washed with 40 mL of ethanol and dried under reduced pressure. The recrystallization procedure is then repeated twice using the same volumes of solvents (230 mL of water and 230 mL of ethanol) to give 23-25 g (63-69%) of the tartrate salt as colorless crystals, $[\alpha]_D^{23} -10.8 \pm 0.2^\circ$ (H₂O, c 1.3), lit.⁵ $[\alpha]_D^{23} -11^\circ$ (H₂O).

The salt is transferred to a 1-L, one-necked, round-bottomed flask equipped with a magnetic stirring bar and suspended in 300 mL of water. After the mixture is vigorously stirred and then cooled to 0-5°C, 23 mL of 50% aqueous sodium hydroxide is added dropwise followed by 150 mL of dichloromethane, and stirring is continued for 30 min. The phases are separated, the aqueous phase is washed twice with 50 mL of dichloromethane and the combined organic extracts are washed with brine, dried

over anhydrous sodium sulfate and filtered. Removal of the volatile material under reduced pressure gives a colorless solid that is recrystallized from hexane to yield 12-14 g (57-66%) of (S,S)-(-)-diamine as colorless crystals, $[\alpha]_D^{23} -106 \pm 1^\circ$ (MeOH, c 1.1) lit.⁶ $[\alpha]_D^{23} -106.5^\circ$ (MeOH, c 1.09) (Note 14).

The filtrates from all crystallizations are combined and the solvent is evaporated on a rotary evaporator under vacuum (water aspirator). The residual solid is transferred to a 1-L, one-necked, round-bottomed flask equipped with a magnetic stirring bar, and suspended in 250 mL of water. To this vigorously stirred mixture is slowly added 25 mL of aqueous 50% sodium hydroxide followed by 200 mL of dichloromethane and the stirring is continued for 30 min. The phases are separated, the aqueous phase is washed twice with 50 mL of dichloromethane and the combined organic extracts are washed with brine, dried over anhydrous sodium sulfate and filtered. Removal of volatile material under reduced pressure gives 24-27 g of the enriched (R,R)-diamine as pale yellow crystals. This material is treated with (D)-(-)-tartaric acid (Note 12) and the resulting salt is recrystallized in exactly the same manner as described for the other enantiomer to give 29-31 g (80-85%) of colorless crystals, $[\alpha]_D^{23} +4 \pm 0.5^\circ$ (H₂O, c 1.3). (The checkers found that the salt from (-)-tartaric acid was optically impure even after five recrystallizations. However, this did not affect the optical purity of the (R,R)-(+)-diamine.) Treatment with sodium hydroxide, as described above, followed by crystallization from hexane gives 11.5-13 g (54-61%) of (R,R)-(+)-diamine as colorless crystals, $[\alpha]_D^{23} +106 \pm 1^\circ$ (MeOH, c 1.1) (Note 14).

2. Notes

1. Step A is a modified literature procedure.³
2. Glacial acetic acid (99.8%), benzil (99%), anhydrous ammonium acetate (A.C.S.) and cyclohexanone (99.8%) were obtained from the Aldrich Chemical Company, Inc., and used as received.
3. As the reaction progresses there is a change of color from light yellow to dark green.
4. This material is pure enough for use in the next step. If necessary, it can be recrystallized from hexane or methanol-water. The properties of 2,2-spirocyclohexane-4,5-diphenyl-2H-imidazole are as follows: $R_f = 0.48$ (hexane-ether 1:1, v/v); ^1H NMR (CDCl_3) δ : 1.65-1.92 (m, 6 H), 1.95-2.00 (m, 4 H), 7.33-7.53 (m, 10 H); ^{13}C NMR (CDCl_3) δ : 24.1, 25.7, 34.7, 104.1, 128.3, 128.9, 129.9, 133.1, 164.0.
5. Reagent grade tetrahydrofuran purchased from J. T. Baker Chemical Co., was freshly distilled from sodium metal and benzophenone.
6. Anhydrous ammonia (99.98%) was obtained from Matheson Gas Products, Inc., and used as received.
7. The mixture stays homogeneous when cooled to -78°C .
8. Lithium wire (99% with 1% of sodium) was purchased from the Aldrich Chemical Company, Inc. The mineral oil is wiped off with a paper towel before use.
9. Absolute ethanol (200 proof) was obtained from Aaper Alcohol and Chemical Co. and used as received.
10. The racemic diamine contains 5-10% of an impurity (by ^{13}C NMR analysis) that does not interfere with the subsequent resolution. The product has the following spectral properties: ^1H NMR (400 MHz, CDCl_3) δ : 1.59 (bs, 4 H), 4.10 (s, 2 H), 7.2-7.3 (m, 10 H); ^{13}C NMR (100 MHz, CDCl_3) δ : 61.9, 126.8, 126.9, 128.2, 143.4.

11. This resolution procedure is essentially the same as described in the literature.⁵

12. (L)-(+)- and (D)-(-)-Tartaric acids (99+ and 99%, respectively) were obtained from the Aldrich Chemical Company, Inc., and used as received.

13. The tartaric acid solution should be added slowly to avoid spontaneous boiling of ethanol.

14. The spectral properties of this product are the same as that of the racemate (see Note 10). The optical purity is higher than 98% as confirmed by ¹H NMR of its salt with (L)-mandelic acid.⁷

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

Enantiomerically pure (+)- and (-)-diphenylethylenediamines have recently been used for highly stereoselective Diels-Alder,⁸ aldol,⁸ allylation,⁹ osmylation,¹⁰ and epoxidation¹¹ reactions. Other synthetic applications involve enantioselective Michael addition¹² and asymmetric hydrogenation.¹³

The present two-step procedure for preparation of the racemic diphenylethylenediamine is significantly shorter and more suitable for scale-up than that described in the literature.⁴ The resolution of the racemate has also been reported using the commercially available enantiomers of mandelic acid.⁶

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2. Department of Chemistry, Harvard University, Cambridge, MA 02138.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(1R,2R)-(+)-1,2-Diphenyl-1,2-ethylenediamine: 1,2-Ethylenediamine, 1,2-diphenyl-,
[R-(R*,R*)]- (9); (35132-20-8)

(1S,2S)-(-)-1,2-Diphenyl-1,2-ethylenediamine: Ethylenediamine,
1,2-diphenyl-, (1S,2S)-(-)- (8); 1,2-Ethylenediamine, 1,2-diphenyl-,
[S-(R*,R*)]- (9); (29841-69-8)

2,2-Spirocyclohexane-4,5-diphenyl-2H-imidazole:

1,4-Diazaspiro[4.5]deca-1,3-diene, 2,3-diphenyl- (9); (5396-98-5)

Benzil (8); Ethanedione, diphenyl- (9); (134-81-6)

Cyclohexanone (8,9); (108-94-1)

(±)-1,2-Diphenyl-1,2-ethylenediamine: Ethylenediamine, 1,2-diphenyl-, (±)- (8);
1,2-Ethylenediamine, 1,2-diphenyl-, (R*,R*)-(±)- (9); (16635-95-3)

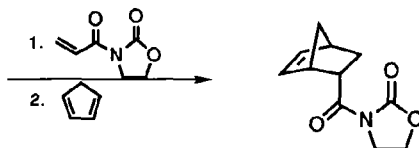
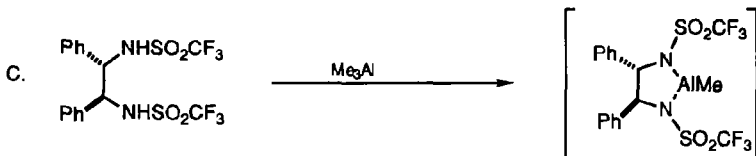
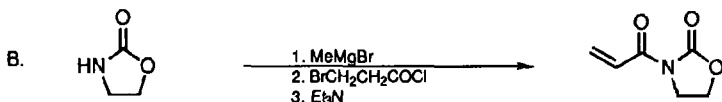
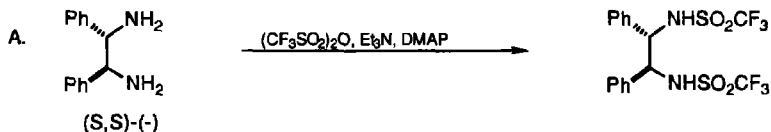
Lithium (8,9); (7439-93-2)

L-Tartaric acid: Tartaric acid, L- (8); Butanedioic acid, 2,3-dihydroxy-,
[R-(R*,R*)]- (9); (87-69-4)

D-(-)-Tartaric acid: Tartaric acid, D-(-)- (8); Butanedioic acid, 2,3-dihydroxy-,
[S-(R*,R*)]- (9); (147-71-7)

**ENANTIOSELECTIVE, CATALYTIC DIELS-ALDER REACTION:
(1S-endo)-3-(BICYCLO[2.2.1]HEPT-5-EN-2-YLCARBONYL)-
2-OXAZOLIDINONE**

(2-Oxazolidinone, 3-bicyclo[2.2.1]hept-5-en-2-ylcarbonyl)-, (1S-endo)-



Submitted by S. Pikul¹ and E. J. Corey.²

Checked by Scott Jeffrey and James D. White.

1. Procedure

A. Bistriflamide of (1S,2S)-1,2-diphenylethylenediamine. A 50-mL, one-necked, round-bottomed flask, equipped with a magnetic stirring bar, is charged with 1.06 g (5 mmol) of (1S,2S)-1,2-diphenylethylenediamine (Note 1), 2.1 mL (15 mmol) of triethylamine (Note 2), 12.2 mg (0.1 mmol) of 4-dimethylaminopyridine (DMAP) (Note 3) and 25 mL of methylene chloride (Note 4). The mixture is stirred to dissolve the solids, cooled to -78°C with a solid carbon dioxide/acetone bath, and 3.39 g (12 mmol) of trifluoromethanesulfonic anhydride (Note 5) is added dropwise. The cooling bath is removed and the mixture is allowed to warm to ambient temperature over 30 min. The mixture is then poured into 4% aqueous sodium bicarbonate, the phases are separated, and the aqueous phase is washed with 15 mL of methylene chloride. The combined organic phases are washed with 1 N hydrochloric acid, with brine, and then dried over anhydrous sodium sulfate and filtered. The filtrate is concentrated under reduced pressure and the residue is subjected to flash chromatography³ on 100 g of silica gel (Note 6) (15% ethyl acetate-hexane, v/v) to give 1.64 g (69%) of the bistriflamide of (1S,2S)-1,2-diphenylethylenediamine as colorless crystals, mp 213-214°C (Note 7).

B. Acryloyl-2-oxazolidinone (Note 8). A flame-dried, 1-L, one-necked, round-bottomed flask, equipped with a magnetic stirring bar, is charged with 8.71 g (100 mmol) of 2-oxazolidinone (Note 3), flushed with argon (Note 9), and then 500 mL of tetrahydrofuran (Note 10) is introduced. The mixture is stirred to dissolve solids, cooled to 0°C, and 33.3 mL (100 mmol) of 3 M methylmagnesium bromide in ether (Note 3) is slowly added. After the solution is stirred for 10 min at 0°C, 11.6 mL (115 mmol) of 3-bromopropionyl chloride (Note 11) is added dropwise. The cooling bath is removed and the mixture is allowed to warm to ambient temperature over 30 min. The mixture is diluted with 600 mL of peroxide-free ether (Note 12) and washed with

saturated aqueous ammonium chloride. The organic phase is dried over magnesium sulfate and filtered. To the filtrate, stirred at ambient temperature, is added 69 mL (500 mmol) of triethylamine (Note 2). A colorless precipitate forms immediately and the resulting slurry is stirred at ambient temperature for 3 hr, then poured into a 1:1 mixture of saturated aqueous ammonium chloride and 1 N aqueous hydrochloric acid. The aqueous layer is extracted with 200 mL of peroxide-free ether (Note 12), and the combined organic phases are dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue is subjected to flash chromatography³ on 150 g of silica gel (Note 6) (35% ethyl acetate-hexane, v/v) to give 5.81 g (41%) of acryloyl-2-oxazolidinone as colorless crystals, mp 82-83°C (Note 13).

C. Diels-Alder reaction. All reagents and glassware are dried rigorously. A flame-dried, 250-mL, three-necked, round-bottomed flask, equipped with a magnetic stirring bar and a reflux condenser, is charged with 1.31 g (2.75 mmol) of bistriflamide of (1S,2S)-1,2-diphenylethylenediamine (dried at 80°C and 1 mm) and placed under dry argon (Note 9). 1,2-Dichloroethane (20 mL) (Note 14) is added, the mixture is heated to 80°C with stirring to effect solution, cooled to ambient temperature, and treated dropwise with 1.37 mL (2.74 mmol) of 2 M trimethylaluminum in toluene (Note 3). After the evolution of gases ceases, the homogeneous mixture is heated to 80°C (oil bath) for 3 hr. The heating bath is removed, the mixture is cooled to ambient temperature, the reflux condenser is replaced by a glass stopper, and the solvent is removed under reduced pressure (oil pump) that is maintained for an additional 30 min. The resulting solid is dissolved in 10 mL of dry methylene chloride (Note 4) and overlaid with 50 mL of dry heptane. Colorless crystals are deposited after 20 hr. The supernatant liquid is drawn off by syringe and the residual solid is dissolved in 50 mL of methylene chloride (Note 4). The solution is cooled to -78°C and a solution of 7.76 g (55 mmol) of acryloyl-2-oxazolidinone in 50 mL of methylene chloride (Note 4)

is introduced through a cannula. The mixture is stirred for 5 min at -78°C and then 5.7 mL (71 mmol) of neat, cold (-78°C) cyclopentadiene (Note 15) is slowly introduced through a cannula (Note 16) along the cooled sides of the flask. Stirring is continued for another 15 min. The mixture is poured into 1 N aqueous hydrochloric acid, the phases are separated, and the aqueous phase is washed with 25 mL of methylene chloride. The combined organic phases are washed successively with aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate is concentrated under reduced pressure and the residue, is subjected to flash chromatography³ on 150 g of silica gel (Note 6) (hexane-ethyl acetate 2:1, v/v) to give 10.1 g (89%) of the cycloadduct as colorless crystals, mp $68-69^{\circ}\text{C}$ (Note 17 and 18).

2. Notes

1. (1S,2S)-1,2-Diphenylethylenediamine is prepared according to the preceding procedure.

2. Triethylamine (99+%) was purchased from the Aldrich Chemical Company, Inc., and stored over sodium hydroxide.

3. 4-Dimethylaminopyridine (DMAP) (99%), 2-oxazolidinone (98%), methylmagnesium bromide (3 M in ether), and trimethylaluminum (2 M in toluene) were purchased from the Aldrich Chemical Company, Inc., and used as received.

4. Methylene chloride (A.C.S. reagent) was distilled from calcium hydride prior to use.

5. Trifluoromethanesulfonic anhydride was purchased from the Aldrich Chemical Company, Inc., and used as received. It can also be prepared from the acid according to the *Organic Syntheses* procedure.⁴

6. Kieselgel 60 (230-400 mesh) was purchased from EM Science, an affiliate of E. Merck, Darmstadt.

7. The product has the following properties: $[\alpha]_D -6.6^\circ$ (CHCl_3 , c 1.4); ^1H NMR (CDCl_3) δ : 4.81 (s, 2 H), 6.80 (bs, 2 H), 7.25 (6 H), 7.0 (4 H); ^{13}C NMR (CDCl_3) δ : 63.7, 127.0, 129.1 (2 C), 135.1.

8. This procedure is essentially the same as that described in the literature.⁵

9. This procedure involves three consecutive evacuations of the flask and fillings with dry argon.

10. Reagent grade tetrahydrofuran purchased from J. T. Baker Chemical Company, was freshly distilled from sodium metal and benzophenone.

11. 3-Bromopropionyl chloride (tech) was purchased from the Aldrich Chemical Company, Inc., and distilled prior to use.

12. Anhydrous diethyl ether was freshly distilled from sodium metal and benzophenone.

13. The product has the following properties: $R_f = 3.1$ (35% ethyl acetate in hexane, v/v); IR cm^{-1} : 1785, 1675, 1419, 1396, 1321, 1258, 1220, 1024, 1008, 982, 752; ^1H NMR (CDCl_3) δ : 4.09 (t, 2 H, $J = 8.0$), 4.45 (t, 2 H, $J = 8.0$), 5.90 (dd, 1 H, $J = 10.4, 1.6$), 6.56 (dd, 1 H, $J = 17.1, 1.6$), 7.49 (dd, 1 H, $J = 17.1, 10.4$); ^{13}C NMR (CDCl_3) δ : 42.6, 62.1, 127.0, 131.6, 153.6, 165.0.

14. 1,2-Dichloroethane (99%, A.C.S. reagent) was freshly distilled from calcium hydride.

15. Cyclopentadiene was prepared by thermal cracking of dicyclopentadiene available from the Aldrich Chemical Company, Inc., following the literature procedure.⁶

16. Because of the high rate of the cycloaddition reaction it is very important that the cyclopentadiene solution enter the reaction flask and mix with the acrylate solution at as low a temperature as possible. For this reason it is beneficial to use a short cannula and to introduce the cyclopentadiene solution onto the wall of the flask that is deeply immersed in a solid CO_2 bath.

17. The product has the following properties: $[\alpha]_D -152.0^\circ$ (CHCl_3 , c 1.5; ee 89%), (lit.⁷ $[\alpha]_D -65^\circ$ (CHCl_3 , c 1.5; ee 38%); $R_f = 0.23$ (hexane-ethyl acetate 2:1, v/v); IR cm^{-1} : 2975, 1775, 1696, 1386, 1337, 1279, 1253, 1226, 1111, 1039, 761, 704; ^1H NMR (CDCl_3) δ : 1.39-1.50 (m, 3 H), 1.95 (ddd, 1 H, $J = 12.6, 9.3, 3.7$), 2.93 (m, 1 H), 3.30 (m, 1 H), 3.91-4.00 (m, 3 H), 4.35-4.41 (m, 2 H), 5.87 (dd, 1 H, $J = 5.5, 2.8$), 6.24 (dd, 1 H, $J = 5.5, 3.1$); ^{13}C NMR (CDCl_3) δ : 29.5, 42.9 (2 C), 43.2, 46.4, 50.2, 61.9, 131.6, 138.1, 153.4, 174.7.

18. The endo-exo selectivity of the cycloaddition reaction is higher than 50:1, since no signals corresponding to the exo product are observed in the 500 MHz ^1H NMR spectrum of the crude or chromatographed product. The optical purity is 89% ee based on comparison with an authentic sample and the literature data.⁷ The optical purity is confirmed by a 500 MHz ^1H NMR spectrum of the corresponding Mosher ester prepared in two steps: 1. Lithium aluminum hydride (LiAlH_4) reduction in tetrahydrofuran at room temperature; 2. esterification of the resulting primary alcohol with (R)-(+)- α -methoxy- α -(trifluoromethyl)phenylacetyl chloride⁸ in the presence of triethylamine and DMAP in methylene chloride at room temperature.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

The design and application of chiral, non-racemic Lewis acids for the asymmetric Diels-Alder reaction has recently been a subject of considerable interest.⁹ Several methods have been developed in many laboratories^{7,10} but catalysts are still needed that are more efficient in governing the stereochemical course of the cycloaddition reaction.

This procedure describes the preparation and application of an effective chiral catalyst for the enantioselective Diels-Alder reaction.¹¹ The catalyst is derived from optically active 1,2-diphenylethylenediamine, the preparation of which (either antipode) was described in the preceding procedure. The aluminum-based Lewis acid also catalyzes the cycloaddition of crotonoyl oxazolidinones with cyclopentadiene,¹¹ and acryloyl derivatives with benzyloxymethylene-cyclopentadiene. The latter reaction leads to optically pure intermediates for synthesis of prostaglandins.¹¹

1. Miami Valley Laboratories, The Procter & Gamble Company, Cincinnati, OH 45239.
2. Department of Chemistry, Harvard University, Cambridge, MA 02138.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(1S-endo)-3-(Bicyclo[2.2.1]hept-5-en-2-ylcarbonyl)-2-oxazolidinone:

2-Oxazolidinone, 3-(bicyclo[2.2.1]hept-5-en-2-ylcarbonyl)-, (1S-endo)- (12);
(109299-97-0)

(1S,2S)-1,2-Diphenylethylenediamine bistriflamide: Methanesulfonamide, N,N'-(1,2-diphenyl-1,2-ethanediy)bis[1,1,1-trifluoro-, [S-(R*,R*)]- (12); (121788-77-0)

(1S,2S)-(-)-1,2-Diphenylethylenediamine: Ethylenediamine, 1,2-diphenyl-, (1S,2S)-(-)- (8); 1,2-Ethanediamine, 1,2-diphenyl-, [S-(R*,R*)]- (9); (29841-69-8)
Triethylamine (8); Ethanamine, N,N-diethyl- (9); (121-44-8)

4-Dimethylaminopyridine: Pyridine, 4-(dimethylamino)- (8); 4-Pyridinamine, N,N-dimethyl- (9); (1122-58-3)

Trifluoromethanesulfonic anhydride: Methanesulfonic acid, trifluoro-, anhydride (8,9); (358-23-6)

Acryloyl-2-oxazolidinone: 2-Oxazolidinone, 3-acryloyl- (8,9); (2043-21-2)
2-Oxazolidinone (8,9); (497-25-6)

Methylmagnesium bromide: Magnesium, bromomethyl- (9); (75-16-1)

3-Bromopropionyl chloride: Propionyl chloride, 3-bromo- (8); Propanoyl chloride, 3-bromo- (9); (15486-96-1)

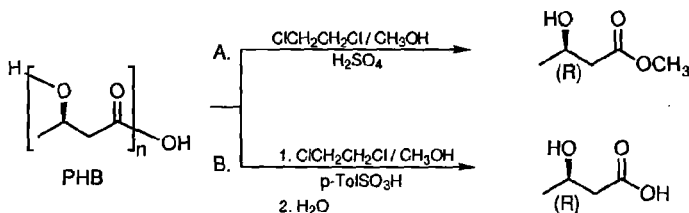
1,2-Dichloroethane: Ethane, 1,2-dichloro- (8,9); (107-06-2)

Trimethylaluminum: Aluminum, trimethyl- (9); (75-24-1)

Cyclopentadiene: 1,3-Cyclopentadiene (8,9); (542-92-7)

DIRECT DEGRADATION OF THE BIOPOLYMER POLY[(R)-3-HYDROXYBUTYRIC ACID] TO (R)-3-HYDROXYBUTANOIC ACID AND ITS METHYL ESTER

(Butanoic acid, 3-hydroxy-, (R)-, homopolymer to Butanoic acid, 3-hydroxy-, (R)- and Butanoic acid, 3-hydroxy-, methyl ester, (R)-)



Submitted by Dieter Seebach, Albert K. Beck, Richard Breitschuh, and Kurt Job.¹

Checked by Eugene R. Hickey and Leo A. Paquette.

1. Procedure

A. (R)-(-)-Methyl 3-hydroxybutanoate. A 2-L, round-bottomed flask is charged with 50 g (0.58 mol) of poly-[(R)-3-hydroxybutyric acid] (PHB) (Note 1) and 500 mL of absolute 1,2-dichloroethane. The flask is equipped with a reflux condenser, and the mixture is heated at reflux for 1 hr. A solution of 10 mL of concd sulfuric acid in 200 mL of absolute methanol is added and the reaction mixture is heated at reflux for 3 days. During this time the mixture becomes homogeneous.

After the reaction mixture is cooled to room temperature, 100 mL of half-saturated brine is added to the reaction mixture, which is stirred for 10 min before the layers are separated. The aqueous layer is extracted three times with 200 mL each of

chloroform. The combined organic layers are washed with 100 mL of brine, 100 mL of saturated sodium bicarbonate solution, and 100 mL of brine. After the solution is dried over magnesium sulfate and removed in a rotary evaporator, a residue of 59 g is isolated.

This crude product is distilled under reduced pressure to give 48 g (70%) of pure (R)-(-)-methyl 3-hydroxybutanoate (bp 61-62°/18 mm) with a specific rotation of $[\alpha]_D^{25} -47.6^\circ$ (CHCl₃, c 1.0) (Note 2).

B. (R)-(-)-3-Hydroxybutanoic acid. In a 1-L, two-necked, round-bottomed flask, fitted with a precision-ground stirrer and a coil condenser bearing a distillation bridge, are placed 200 mL of 1,2-dichloroethane and 50 g (0.58 mol) of PHB (Note 1). The mixture is stirred and heated at 150°C until a milky solution is formed (Note 3). *p*-Toluenesulfonic acid monohydrate (2.5 g, 0.013 mol) is added and the solution heated an additional 30 min at 150°C. A total amount of 9.3 g (11.8 mL, 0.29 mol) of methanol is then added carefully through the condenser to the boiling solution in approx 1-mL portions (Note 4). The light brown, cloudy solution is heated at reflux (oil bath, 140°C) for another 48 hr (Note 5). The oil bath temperature is reduced to 130°C and 60 mL of water is carefully added. The resulting two-phase mixture is heated for another 4 hr (Note 6). Methanol, 1,2-dichloroethane, and approx 150 mL of water are removed by distillation through the condenser within 1-2 hr (Note 7). During the distillation nine 30-mL portions of water are added; the resulting homogeneous aqueous solution is heated at reflux for another 4 hr. During this period the temperature of the oil bath is increased to 180°C. Methanol/water (50 mL) is removed by distillation and, after the addition of 50 mL of water (Note 8), the solution is again heated at reflux for 15 hr. The reaction mixture is cooled to about 30°C, followed by the addition of 0.6 g (0.015 mol) of sodium hydroxide in 10 mL of water. Water is first removed in a rotary evaporator at a maximum temperature of 30°C, 15 mm, followed by drying at 0.1 mm (Note 9). The

residue is dissolved in 250 mL of ether, the solution is dried over magnesium sulfate, filtered, concentrated in a rotary evaporator and dried at 0.1 mm. The resulting light-brown clear oil (Note 10) is distilled at 80-100°C (air bath)/10⁻³ mm by bulb to bulb distillation (Note 11). The crude product is either crystalline or a colorless oil that crystallizes upon standing at room temperature. After the crystals are crushed in a mortar, they are dried for 2 days in a desiccator over phosphorus pentoxide (P₂O₅) (Note 12), to yield 32 g (53%) of (R)-3-hydroxybutanoic acid, mp 44-46°C [α]_D^{RT} -24.7° (H₂O, c 5.0 (Notes 13, 14, 15).

2. Notes

1. The submitters used PHB=Poly-(R)-3-hydroxybutyric acid obtained from Marlborough Biopolymers Ltd., Rudby Hall, Hutton Rudby, Yarm, Cleveland, England, PHB homopolymer, BX GO4, technical grade powder, MBL 100/703. The checkers used PHB from Fluka Chemie AG, CH-8470 Buchs, Switzerland. The submitters report that the procedure works well on batch sizes of 200-250 g.

2. The spectroscopic properties are as follows: IR (neat) cm⁻¹: 1735 (C=O); ¹H NMR (90 MHz, CDCl₃) δ : 1.25 (d, 3 H, CH₃), 2.45 (d, 2 H, CH₂), 3.00 (br s, 1 H, OH), 3.75 (s, 3 H, OCH₃), 4.20 (m, 1 H, CH). For further data see ref. 2.

3. The submitters used an oil bath to insure vigorous reflux. The time required to obtain the desired solution consistency depends on the PHB used (30 min to over 2 hr).

4. The reaction solution should be maintained at a vigorous reflux. Should the solution cool during the addition a white flaky precipitate may form that redissolves upon extended heating (up to 4 hr at 140°C).

5. This results in a mixture of oligomeric methyl esters with an average degree of polymerization of 2.1-2.3, according to ^1H NMR analysis (ratio of the CH_3C -signals vs. CH_3O -signals of the esters).

6. Most of the methyl ester groups are saponified with release of methanol.

7. It is crucial that all the methanol and 1,2-dichloroethane be removed from the reaction mixture to insure that all the oligomers are in the aqueous phase.

8. Newly formed methanol is removed at this stage. Only a small amount of methyl esters remains in the mixture at this point.

9. Low temperature during evaporation avoids condensation back to oligomers.

10. According to ^1H NMR analysis the crude product consists of more than 93% monomeric (R)-3-hydroxybutanoic acid, contaminated by 1-2% of methyl (R)-3-hydroxybutanoate and less than 0.2% of crotonic acid.

11. The crude product is placed in a 1-L, round-bottomed flask and distilled in an Aldrich Kugelrohr apparatus, heated with an air bath, the receiver bulb being cooled with ice water. Partial condensation of (R)-3-hydroxybutanoic acid to oligomers occurs if the temperature is too high during distillation (Note 12).

12. Drying in an evacuated desiccator over P_2O_5 removes water as well as methyl (R)-3-hydroxybutanoate and crotonic acid.

13. The spectra are as follows: IR (neat) cm^{-1} : 1710 ($\text{C}=\text{O}$); ^1H NMR (90 MHz, CDCl_3) δ : 1.25 (d, 3 H, CH_3), 2.50 (d, 2 H, CH_2), 4.20 (m, 1 H, CH), 7.70 (br s, 2 H, OH). For further data see ref. 2.

14. The distillation residue (8-9 g) consists of water-soluble oligomers that can be saponified without loss of optical purity by heating at reflux with aqueous acid for 15 hr.

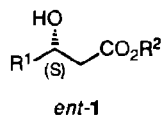
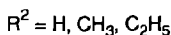
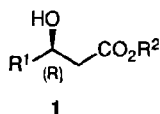
15. The submitters report a yield of 45-48 g (74.5-79%) using PHB obtained from Marlborough Biopolymers. The checkers verified this result using PHB obtained from the submitters. The yield reported here represents the checker's results with PHB obtained from Fluka Chemie.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

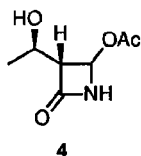
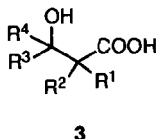
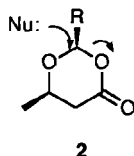
3. Discussion

Optically active 3-hydroxybutanoic acid and its methyl ester were first prepared by McKenzie, Magnus-Levy, and Emil Fischer.³ The biopolymer PHB and mixed polymers containing (R)-3-hydroxybutanoate and (R)-3-hydroxypentanoate were also discovered long ago,^{4,5} and are now produced on an industrial scale.^{6,7} As described here, depolymerization by transesterification [H^+ or $Ti(OR)_4$ catalysis], or by hydrolysis, produces^{8,9} the corresponding monomeric (R)-esters and (R)-acids **1**. The 3-hydroxybutanoic acid can also be prepared by hydrolysis of the ester.^{2,10}



The enantiomeric compounds, *ent-1*, are available from **1** by inversion through sulfonates¹¹ or through β -lactones.¹² Ethyl (S)-3-hydroxybutanoate of 86-95 % ee has

also been made by yeast reduction of acetoacetate.¹³ Either the ester **1** or ent-**1** can be prepared by enantioselective hydrogenation of the methyl acetoacetate with a Ru-BINAP catalyst.¹⁴



The hydroxy acid derivatives **1** are most versatile auxiliaries and building blocks for the synthesis of enantiomerically pure products.^{7a,9b,15} Thus, in an improvement of Johnson's method,¹⁶ the dioxanones **2** can be used for overall enantioselective nucleophilic additions to aldehydes.¹⁷ Through open-chain¹⁸ or cyclic¹⁹ lithium enolates derived from **1** and, through dioxinones,²⁰ new substituents can be introduced at carbons (2), (3) and (4) of hydroxybutanoic or hydroxypentanoic acid to give enantiomerically pure products **21,22** of type **3**. Another application is the incorporation of (R)-3-hydroxybutanoic acid into the antibiotic thienamycin **23** through the β -lactam **4**.

1. Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Zentrum, Universitätstrasse 16, CH-8092 Zürich, Switzerland.
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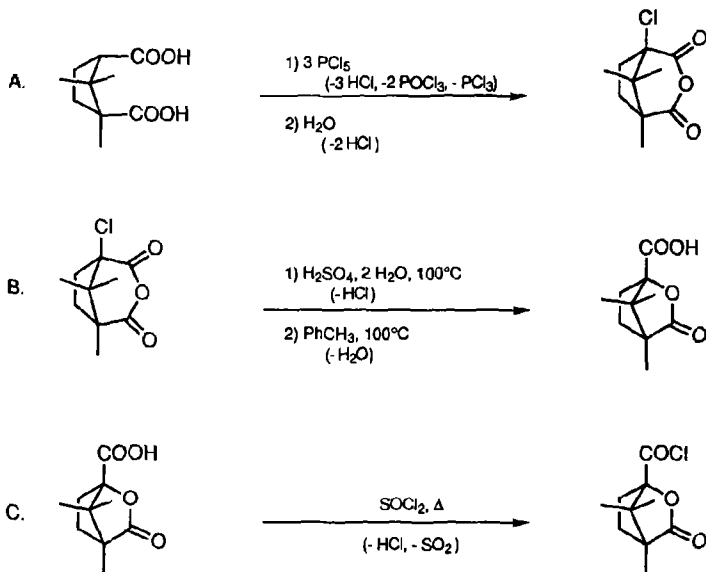
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Poly-[(R)-3-hydroxybutyric acid], PHB: Butyric acid, 3-hydroxy-, D-(-)-, polyesters (8);
Butanoic acid, 3-hydroxy-, (R)-, homopolymer (9); (29435-48-1)
(R)-3-Hydroxybutanoic acid: Butyric acid, 3-hydroxy-, (-)- (8); Butanoic acid, 3-
hydroxy-, (R)- (9); (625-72-9)
(R)-(-)-Methyl 3-hydroxybutanoate: Butyric acid, 3-hydroxy-, methyl ester, D-(-)- (8);
Butanoic acid, 3-hydroxy-, methyl ester, (R)- (9); (3976-69-0)
p-Toluenesulfonic acid monohydrate (8); Benzenesulfonic acid, 4-methyl-,
monohydrate (9); (6192-52-5)

(-)-(1S,4R)-CAMPHANOYL CHLORIDE
(2-Oxabicyclo[2.2.1]heptane-1-carbonyl chloride,
4,7,7-trimethyl-3-oxo-, (1S)-)



Submitted by Hans Gerlach,¹ Dag Kappes, Robert K. Boeckman, Jr.,² and
 Graham N. Maw.

Checked by D. Zhao, D. Hughes, and I. Shinkai.

1. Procedure

A. *(-)-(1R,3R)-3-Chlorocamphoric anhydride*. *(+)-(1R,3S)-Camphoric acid* (Note 1), (125 g, 0.625 mol) is added in small portions to a 1000-mL, three-necked flask charged with 455 g of phosphorus pentachloride (2.19 mol) and equipped with a ground glass adaptor connected to a T-tube with one outlet open to the atmosphere and the remaining outlet connected to a gas trap (Note 2). The mildly exothermic reaction is controlled by gently swirling the flask in an ice bath as required (Note 3). After the addition is complete, the flask is equipped with a reflux condenser topped by a calcium chloride (CaCl_2) drying tube, and the reaction mixture is heated under reflux (using an oil bath at 125°C) for 12 hr. The reaction mixture is cooled to room temperature and the volatile material is removed by distillation using a bath temperature of 50°C under aspirator vacuum with the distillate boiling at $30\text{--}35^\circ\text{C}$ (Note 4). The residual liquid is then added to a mechanically-stirred mixture of ice (2 kg) and dimethylformamide (DMF, 125 ml), and stirring is continued until all the ice has melted. The resulting waxy white precipitate is collected by vacuum filtration while cold (2°C), washed with three, 500-mL portions of cold water, and dried under vacuum (Note 5). The crude white solid, *(-)-(1R,3R)-3-chlorocamphoric anhydride* (122 g, 90%), is of sufficient purity to be used in the next step (Notes 6 and 7).

B. *(-)-(1S,4R)-Camphanic acid*. A 2000-mL, three-necked round-bottomed flask equipped with a magnetic stirrer and reflux condenser is charged with 1000-mL of 0.1 N sulfuric acid and heated by means of an oil bath to 80°C . Finely powdered *(-)-(1R,3R)-3-chlorocamphoric anhydride* (115 g, 0.53 mol) is added in portions over about 10 min to the stirred acid solution, the necks are sealed with glass stoppers and the resulting suspension is brought to a gentle reflux (Note 2). After all the solids have dissolved (4-6 hr), the resulting solution is refluxed for an additional 2 hr (Note 8). The solution is allowed to cool to room temperature with stirring overnight (~ 12 hr), and the

resulting off-white solid is collected by vacuum filtration and washed with water (3 x 250 mL). The remaining camphanic acid is obtained by extraction of the aqueous filtrate with three 250-mL portions of chloroform (Note 9). After evaporation of the combined organic phases, the combined vacuum-dried solids are added to a 1000-mL, round-bottomed flask containing 500 mL of toluene, a condenser is added and the mixture is brought to gentle reflux until dissolution is complete (Note 2). The water/toluene azeotrope (85°C) is removed by distillation until no further water is obtained (Note 10). Distillation of the toluene (110°C) is then continued until the residual volume has been reduced to ~350 mL (Notes 10 and 11). The resulting solution is allowed to cool to room temperature during which time the acid crystallizes. After 4 hr at room temperature, the solids are collected by vacuum filtration and air-dried, affording (-)-(1S,4R)-camphanic acid (76 g, 72%) as colorless needles, mp 197-201°C, of sufficient purity for use in the next step (Notes 12 and 13).

C. *(-)-(1S,4R)-Camphanoyl chloride*. A 500-mL, three-necked, round-bottomed flask, equipped for magnetic stirring and protected from moisture by a reflux condenser topped by a CaCl₂ drying tube, is charged with 200 mL of thionyl chloride using a graduated cylinder. (-)-(1S,4R)-Camphanic acid (63.8 g, 0.322 mol) is added in portions using a powder funnel over 30 min, and the reaction mixture is heated under reflux for 3 hr, then allowed to cool to room temperature (Note 2). Excess thionyl chloride is removed by rotary evaporation (Note 14) to afford a solid that is freed of any residual thionyl chloride by the addition of toluene (500 mL) and subsequent evaporation under reduced pressure (repeated three times). The resulting solids are dried under high vacuum (Note 5) to afford 69 g of (-)-(1S,4R)-camphanoyl chloride (99%) as an off-white solid, mp 69-71°C (Notes 15 and 16).

2. Notes

1. (+)-(1R,3S)-Camphoric acid (99% purity) was obtained from Aldrich Chemical Company, Inc.

2. The acidic gases may be absorbed in 10% NaOH solution using the absorption trap as described in *Org. Synth., Coll. Vol. I* 1941, 97.

3. The reactants initially form a paste that may form sizable lumps upon agitation, but the mixture liquifies upon further reaction as the result of the production of phosphorus oxychloride (POCl_3) and phosphorus trichloride (PCl_3).

4. The resulting liquid sometimes contains small amounts of white solid, but this solid does not require removal by filtration.

5. A freeze dryer (lyophilizer) was employed for vacuum drying (23°C at ~ 0.05 mm).

6. If desired, a pure sample of the anhydride (mp $225\text{--}229^\circ\text{C}$) can be obtained by recrystallization of the crude anhydride from carbon tetrachloride (CCl_4) (1 g/5 mL).

7. Spectroscopic data for the purified anhydride are as follows: ^1H NMR (300 MHz, CDCl_3) δ : 1.07 (s, 3 H), 1.14 (s, 3 H), 1.36 (s, 3 H), 2.11 (m, 2 H), 2.50 (m, 2 H); ^{13}C NMR (75 MHz, CDCl_3) δ : 16.0, 17.9, 18.7, 31.5, 35.2, 48.7, 54.1, 166.0, 170.3; IR (cm^{-1}): 3019, 1821, 1773, 1215; $[\alpha]_{\text{D}}^{25} -17.6^\circ$ (chloroform, c 2.04).

8. A total period of heating of 6-8 hr at $80\text{--}100^\circ\text{C}$ was required.

9. Alternatively, a second crop of material can be obtained from the aqueous filtrate after several hours. However, a considerable amount of camphanic acid still remains in the aqueous layer; thus chloroform extraction of the aqueous phase as described is recommended. *To avoid undue exposure to the chloroform vapor, these extractions should be performed in a fume hood.*

10. The volume of toluene required will depend on the amount of water in the crude material. Additional toluene should be added as required, so that the final, residual volume of dry toluene solution is ~350 mL as described.

11. Colored impurities, if produced, can be removed by treatment of the solution, prior to cooling, with charcoal (Norit) followed by filtration.

12. If desired, pure acid (mp 201-204°C) can be obtained by recrystallization of the crude acid from hot toluene.

13. Spectroscopic data for the purified acid are as follows: ^1H NMR (300 MHz, CDCl_3) δ : 1.03 (s, 3 H), 1.11 (s, 3 H), 1.15 (s, 3 H), 1.74 (ddd, 1 H, $J = 4.3, 9.3$, and 13.2), 1.98 (ddd, 1 H, $J = 4.5, 10.6$, and 13.2), 2.11 (ddd, 1 H, $J = 4.5, 9.3$, and 13.5), 2.48 (ddd, 1 H, $J = 4.2, 10.6$, and 13.5), 8.80 (br, 1 H, (s)); ^{13}C NMR (75 MHz, CDCl_3) δ : 9.60, 16.70, 16.73, 29.02, 30.73, 54.60, 55.11, 90.89, 172.41, 177.90; (IR cm^{-1}): 3418, 3019, 1785, 1716, 1215; $[\alpha]_{\text{D}}^{25} -20.4^\circ$ (dioxane, c 1.71).

14. Corrosive thionyl chloride may destroy the rubber vacuum seals of a rotary evaporator. Thionyl chloride can also be removed by vacuum distillation.

15. (-)-(1S,4R)-Camphanoyl chloride produced in this manner is of sufficient purity to be used directly in most acylation reactions. However, pure acid chloride (mp 69-71°C) can be conveniently obtained by recrystallization of the crude acid chloride from cold CCl_4 (1 g/1 mL, ~75% recovery).

16. Spectroscopic data for the purified acid chloride are as follows: ^1H NMR (300 MHz, CDCl_3) δ : 1.06 (s, 3 H), 1.12 (s, 3 H), 1.15 (s, 3 H), 1.76 (ddd, 1 H, $J = 4.2, 9.3$, and 13.3), 1.99 (ddd, 1 H, $J = 4.6, 10.6$, and 13.3), 2.18 (ddd, 1 H, $J = 4.6, 9.3$, and 13.6), 2.52 (ddd, 1 H, $J = 4.2, 10.6$, and 13.6); ^{13}C NMR (75 MHz, CDCl_3) δ : 9.55, 16.55, 16.64, 28.76, 31.46, 55.40, 55.52, 94.86, 170.87, 176.52; (IR cm^{-1}): 2975, 1794, 1231; $[\alpha]_{\text{D}}^{25} -24.7^\circ$ (chloroform, c 3.57).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

The resolution of alcohols by fractional crystallization or chromatography of diastereoisomeric esters with (-)-camphanic acid was introduced some time ago.³ The method has proven to be both convenient and efficient. A substructure search in the Chemical Abstracts Service (CAS) registry file has shown that more than 500 camphanic acid derivatives have been described in the last two decades. Besides resolution, camphanic acid esters of primary alcohols have been used to distinguish the signals of diastereotopic α -hydrogen atoms in ^1H NMR spectra and to determine the optical purity of α -deutero primary alcohols.⁴ Camphanoates are well suited for characterizing alcohols. They are easily prepared with camphanoyl chloride in pyridine and generally have high melting points.

Because both enantiomers, (+)- and (-)-camphoric acid, are available by oxidation either from natural (+)-D-camphor or from natural (-)-L-borneol, both enantiomers of camphanoyl chloride can be prepared conveniently.^{3,5} The corresponding enantiomers of camphanic acid were described for the first time by Wreden⁶ and Aschan.⁷ The three-step procedure, described above is an adaptation of procedures described by Aschan,⁸ Zelinsky et al.,⁹ Meyer et al.,¹⁰ and Gerlach.³

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2. Department of Chemistry, University of Rochester, Rochester, NY 14627.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(-)-(1S,4R)-Camphanoyl chloride: 2-Oxabicyclo[2.2.1]heptane-1-carbonyl chloride, 4,7,7-trimethyl-3-oxo-, (-)- (9); (39637-74-6)

(-)-(1R,3R)-3-Chlorocamphanic anhydride: 3-Oxabicyclo[3.2.1]octane-2,4-dione, 1-chloro-5,8,8-trimethyl-, (1R)- (11); (87859-84-5)

(+)-(1R,3S)-Camphoric acid: Camphoric acid, cis-(+)- (8);

1,3-Cyclopentanedicarboxylic acid, 1,2,2-trimethyl-, (1R,cis)- (9); (124-83-4)

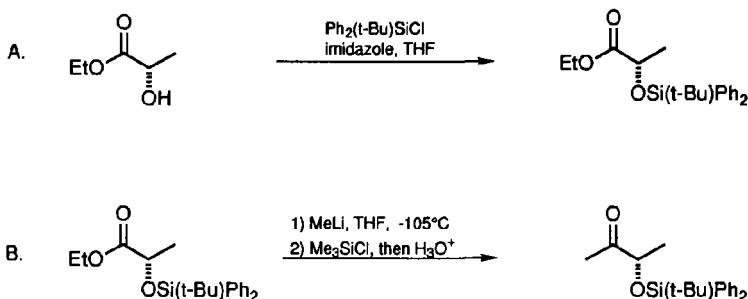
Phosphorus pentachloride: Phosphorus chloride (8); Phosphorane, pentachloro- (9); (10026-13-8)

(-)-(1S,4R)-Camphanic acid: 2-Oxabicyclo[2.2.1]heptane-1-carboxylic acid, 4,7,7-trimethyl-3-oxo-, (-)-(8);

2-Oxabicyclo[2.2.1]heptane-1-carboxylic acid, 4,7,7-trimethyl-3-oxo-, (1S)- (9); (13429-83-9)

Thionyl chloride (8,9); (7719-09-7)

3-(S)-[*(tert*-BUTYLDIPHENYLSILYL)OXY]-2-BUTANONE
(2-Butanone, 3-[[*(1,1*-dimethylethyl)diphenylsilyl]oxy]-, (S)-)



Submitted by Larry E. Overman and Gilbert M. Rishton.¹

Checked by Takashi Ooi and Hisashi Yamamoto.

1. Procedure

A. Preparation of ethyl 2-(S)-[(tert*-butyldiphenylsilyl)oxy]propanoate.* An oven-dried, 500-mL, round-bottomed flask is equipped with a magnetic stirring bar and purged with dry argon. The flask is charged with 10.0 g (84.6 mmol) of (S)-(-)-ethyl lactate, 23.3 g (84.6 mmol) of *tert*-butyldiphenylsilyl chloride, 14.4 g (211 mmol) of imidazole, and 50 mL of dry tetrahydrofuran (Note 1). The resulting, white suspension is stirred vigorously at 23°C for 2 hr. (At the beginning of the stirring, a heated water bath is useful to maintain the reaction temperature.) The mixture is then filtered through glass wool into 400 mL of water and the solids are washed with two 25-mL portions of tetrahydrofuran. The filtrate is concentrated to remove tetrahydrofuran under reduced pressure using a rotary evaporator. The resulting aqueous suspension

is transferred to a 1-L separatory funnel and is extracted with 400 mL of ethyl acetate. The organic phase is washed with two 400-mL portions of water, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure using a rotary evaporator to give 30.0 g (99%) of ethyl 2-(S)-[(*tert*-butyldiphenylsilyl)oxy]propanoate as a clear colorless oil (Note 2).

*B. Preparation of 3-(S)-[(*tert*-butyldiphenylsilyl)oxy]-2-butanone.* An oven-dried 1-L, three-necked, round-bottomed flask is charged with 20.0 g (56.2 mmol) of ethyl 2-(S)-[(*tert*-butyldiphenylsilyl)oxy]propanoate and the flask is fitted with a mechanical stirrer, a 100-mL addition funnel, and a rubber septum. A low temperature thermometer (Note 3) is inserted through the rubber septum and 250 mL of dry tetrahydrofuran (Note 1) is injected with a syringe. The mechanically stirred solution is cooled to -105°C (Note 4) and maintained until the temperature has stabilized. The addition funnel is charged with 52 mL of a 1.4 M ether solution of halide-free methyl lithium (73 mmol) and this solution is added dropwise with mechanical stirring over 35-40 min. The internal temperature is never allowed to warm above -100°C (Note 5). When addition is complete, 20 mL (158 mmol) of trimethylsilyl chloride (Note 6) is injected and the resulting clear solution is warmed to room temperature over 20 min with the aid of a water bath. At this time 200 mL of 1 N hydrochloric acid is added and vigorous stirring is continued for 1 hr (Note 7). The mixture is poured slowly into a 2-L Erlenmeyer flask containing 30 g of solid sodium bicarbonate and then concentrated to remove tetrahydrofuran under reduced pressure using a rotary evaporator. The resulting aqueous suspension is transferred to a 1-L separatory funnel and extracted with 400 mL of ethyl acetate. The organic layer is washed with two 400-mL portions of water, dried over anhydrous sodium sulfate, filtered, and concentrated using a rotary evaporator to give 18.2 g (99%) of 3-(S)-[(*tert*-butyldiphenylsilyl)oxy]-2-butanone as a clear colorless oil (Notes 8 and 9).

2. Notes

1. (S)-Ethyl lactate, $[\alpha]_D^{14} -10^\circ$ (neat) and other chemicals employed in this procedure were obtained from Aldrich Chemical Company, Inc. Anhydrous tetrahydrofuran was prepared by distillation under argon from sodium benzophenone ketyl.

2. Gas chromatographic analysis using a 25-m 10% SP 2100 silicone column showed that this sample was >95% pure and contained one major unidentified impurity. Material of this purity is acceptable for use in the second step. A sample showing no detectable impurities by GLC analysis can be obtained by flash chromatography on silica gel (5:95 ethyl acetate-hexane). This sample has the following spectral characteristics: $[\alpha]_D -45.1^\circ$ (MeOH, c 1.0); ^1H NMR (500 MHz, CDCl_3) δ : 1.09 (s, 9 H, t-Bu), 1.14 (t, 3 H, J = 7.1, OCH_2CH_3), 1.37 (d, 3 H, J = 6.7, CH_3), 3.99-4.04 (m, 2 H, OCH_2CH_3), 4.27 (q, 1 H, J = 6.7, CH), 7.36-7.41 (m, 6 H, Ph), 7.65-7.69 (m, 4 H, Ph); ^{13}C NMR (125 MHz, CDCl_3) δ : 14.0, 19.2, 21.2, 26.8, 60.5, 68.9, 127.6, 129.7, 133.1, 133.5, 135.7, 135.8, 173.6; IR (film) cm^{-1} : 2980, 2933, 2859, 1753, 1735, 1429, 1198, 1139, 1112, 1081, 823, 739, 702, 690, 611. Anal. Calcd for $\text{C}_{21}\text{H}_{28}\text{O}_3\text{Si}$: C, 70.74; H, 7.92. Found: C, 70.94; H, 7.89.

3. An OMEGA 450 ATT (Type T) thermocouple thermometer was used.

4. A minimum amount of liquid nitrogen contained in a 1-L Dewar bowl was used to cool the solution to -105°C .

5. It is crucial that the internal temperature of the reaction mixture never exceed -100°C during the addition of the methyl lithium solution. If the temperature begins to rise, the dropwise addition of the reagent should be slowed. Periodic addition of a small amount of liquid nitrogen to the cooling bath may also be necessary.

6. Trimethylsilyl chloride is distilled from calcium hydride and stored under argon or nitrogen in a stoppered bottle over polyvinylpyridine.

7. Hydrolysis of the reaction mixture may be accomplished by addition of 200 mL of water instead of 200 mL of 1 N hydrochloric acid. In the former case complete hydrolysis requires 5 hr and in the latter hydrolysis is complete within 1 hr.

8. Gas chromatographic analysis using a 25-m 10% SP 2100 silicone column showed that this sample was >95% pure and contained one major unidentified impurity. A sample of 100% purity may be obtained by flash chromatography on silica gel (1:9 ethyl acetate-hexane). This sample has the following spectral characteristics: $[\alpha]_D -3.1^\circ$ (MeOH, c 1.0); ^1H NMR (300 MHz, CDCl_3): δ : 1.10 (s, 9 H, t-Bu), 1.19 (d, 3 H, J = 6.8, CH_3), 2.16 (s, 3 H, COCH_3), 4.17 (q, 1 H, J = 6.8, CH), 7.36-7.40 (m, 6 H, Ph), 7.60-7.66 (m, 4 H, Ph); ^{13}C NMR (75 MHz, CDCl_3) δ : 19.2, 20.6, 24.9, 26.9, 75.7, 127.6, 127.8, 129.9, 135.7, 211.7; IR (film) cm^{-1} : 2961, 2933, 2859, 1719, 1428, 1114, 823, 741, 703, 691; MS (CI) m/z 327.1760 (327.1780 calcd for $\text{C}_{20}\text{H}_{26}\text{O}_2\text{Si}$, MH). Anal. Calcd for $\text{C}_{20}\text{H}_{26}\text{O}_2\text{Si}$: C, 73.57; H, 8.03. Found: C, 73.52; H, 8.07.

9. The enantiomeric excess of the product is >96%. This was determined by treating a sample of the ketone sequentially with methyllithium and tetrabutylammonium fluoride (THF, -78°C). The resulting diol was converted to its Mosher diester² [2.5 eq of (+)- α -methoxytrifluoromethylphenylacetic acid, 3 eq of dicyclohexylcarbodiimide, and 0.2 eq of 4-(dimethylamino)pyridine, CH_2Cl_2] and the crude esterification reaction mixture was analyzed using 500 MHz ^1H NMR. None of the minor diastereomer was observed; doping experiments established that 2% of the minor diastereomer would have been detected [diagnostic signals: δ 5.03 (q, J = 6.2, major diastereomer); δ 5.17 (q, J = 6.1, minor diastereomer)].

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

The sequence detailed here provides 3-(S)-((tert-butylidiphenylsilyl)oxy)-2-butanone in high purity and on a preparative scale from inexpensive (S)-ethyl lactate. This optically active ketone should be a useful intermediate for the preparation of a variety of enantiomerically pure materials. It has been used in our laboratory for an asymmetric synthesis of (+)-muscarine³ and in the preparation of various other optically active tetrahydrofurans.⁴ Mitsunobu inversion of (S)-ethyl lactate followed by protection to provide 2-(R)-((tert-butylidiphenylsilyl)oxy)propanoate⁵ affords, by this method, ready access to the enantiomer of the title compound.

Conversions of carboxylic acids to ketones are typically performed in stepwise fashion⁶ via intermediates such as acid chlorides,⁷ anhydrides,⁸ thioesters,⁹ or N-alkoxy amides,¹⁰ or by the direct reaction of carboxylic acids with lithium reagents.¹¹ In this latter method trimethylsilyl chloride has been shown to be an effective reagent for trapping the tetrahedral alkoxide intermediates and for quenching excess organolithium reagent.

The addition of trimethylsilyl chloride proved crucial to the success of the procedure described here. Use of aqueous ammonium chloride as a quenching reagent (instead of trimethylsilyl chloride) resulted in a reaction mixture that contained up to 30% of the corresponding tertiary alcohol.

Preliminary investigations into the generality of this synthesis of lactate-derived ketones using other alkyl lithium reagents including butyllithium and phenyllithium have not been as successful. Product mixtures were typically contaminated with significant amounts of both the tertiary alcohol and the starting ester.

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

3-(S)-[(*tert*-Butyldiphenylsilyl)oxy]-2-butanone: 2-Butanone, 3-[[[(1,1-dimethylethyl)-diphenylsilyl]oxy]-, (S)- (12); (135367-18-9)

Ethyl 2-(S)-[(*tert*-butyldiphenylsilyl)oxy]propanoate: Propanoic acid, 2-[[[(1,1-dimethylethyl)diphenylsilyl]oxy]-, ethyl ester, (S)- (11); (102732-44-5)

(S)-(-)-Ethyl lactate: Lactic acid, ethyl ester, L- (8); Propanoic acid, 2-hydroxy-, ethyl ester, (S)- (9); (667-47-8)

tert-Butyldiphenylsilyl chloride (Aldrich: *tert*-Butylchlorodiphenylsilane): Silane, chloro(1,1-dimethylethyl)diphenyl- (9); (58479-61-1)

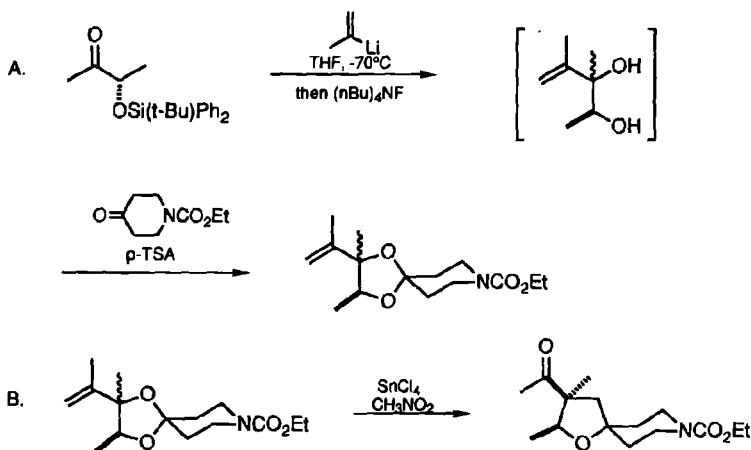
Imidazole (8); 1H-Imidazole (9); (288-32-4)

Ethyl acetate: Acetic acid, ethyl ester (8,9); (141-78-6)

Methylolithium: Lithium, methyl- (8,9); (917-54-4)

Trimethylsilyl chloride (Aldrich: Chlorotrimethylsilane): Silane, chlorotrimethyl- (8,9); (75-77-4)

**STEREOCONTROLLED PREPARATION OF 3-ACYLTETRAHYDROFURANS
FROM ACID-PROMOTED REARRANGEMENTS OF ALLYLIC KETALS:
(2S,3S)-3-ACETYL-8-CARBOETHOXY-2,3-DIMETHYL-1-OXA-8-
AZASPIRO[4.5]DECANE**



Submitted by Larry E. Overman and Gilbert M. Rishton.¹

Checked by Takashi Ooi and Hisashi Yamamoto.

1. Procedure

A. *Preparation of (2R,3S)- and (2S,3S)-1,4-dioxo-2,3-dimethyl-2-(1-methylethenyl)-8-carboethoxy-8-azaspiro[4.5]decane.* An oven-dried, 500-mL, three-necked, round-bottomed flask is fitted with a mechanical stirrer, 100-mL addition funnel, and rubber septum, and then is charged with 100 mL of dry tetrahydrofuran (Note 1) and

7.7 mL (10.5 g, 86.7 mmol) of 2-bromopropene (Note 2). The solution is cooled to -70°C with mechanical stirring and a 1.9 M pentane solution of *tert*-butyllithium (92 mL, 175 mmol) is added by syringe over 20 min. The resulting yellow solution is stirred for an additional 10 min at -70°C and at this time a solution of 17.6 g (54.0 mmol) of 3-(S)-[(*tert*-butyldiphenylsilyl)oxy]-2-butanone² and 50 mL of dry tetrahydrofuran is added by dropping funnel over 20 min. The resulting solution is stirred for an additional 30 min at -70°C and at this time a 1.0 M tetrahydrofuran solution of tetrabutylammonium fluoride (163 mL, 163 mmol) is added in one portion and the resulting mixture is warmed to 23°C and stirred for 1 hr. At this time the contents of the flask are poured into 200 mL of saturated aqueous ammonium chloride (NH₄Cl) and the resulting mixture is concentrated to remove tetrahydrofuran. The resulting aqueous suspension is diluted with 200 mL of brine and extracted twice with 200 mL of ethyl acetate (Note 3). The combined organic extracts are washed with five, 100-mL portions of brine, dried over sodium sulfate, filtered, and then concentrated under reduced pressure using a rotary evaporator. The residue is subjected to short path vacuum distillation (150-160°C, 3 mm) to remove the less volatile *tert*-butyldiphenylsilyl by-product. The distillate contains ca. 10 g of a colorless oil that is comprised of the 2,3-dimethyl-1-pentene-3,4-diols as a 6:1 mixture of diastereomers and up to 30% of tributylamine (Notes 4 and 5).

1-Carboethoxy-4-piperidone (7.52 g, 43.9 mmol) (Note 6) and *p*-toluenesulfonic acid (5.0 g, 26 mmol) are added to a 250-mL, round-bottomed flask that contains the above distillate and a magnetic stir bar. The mixture is stirred under vacuum (20 mm) at 100°C for 90 min and the evolved water vapor is collected in a vacuum trap. The mixture is cooled to 23°C and subjected to flash chromatography on silica gel (250 g, 20 cm x 10 cm) using ethyl acetate:hexane (1:4) as the eluant (Note 7) to give 9.0 g (59% overall) of (2*R*,3*S*)- and (2*S*,3*S*)-1,4-dioxo-2,3-dimethyl-2-(1-methylethenyl)-8-

carboethoxy-8-azaspiro[4.5]decane, a 6:1 mixture of diastereomers, as a pale yellow oil (Note 8).

B. Preparation of (2S,3S)-3-acetyl-8-carboethoxy-2,3-dimethyl-1-oxa-8-azaspiro[4.5]decane. Dry nitromethane (100 mL) (Note 9) is added through a rubber septum by syringe to a vacuum-dried, 500-mL, round-bottomed flask that contains the ketal mixture prepared in Step A (9.00 g, 31.8 mmol) and a magnetic stir bar. The solution is cooled to -23°C, tin(IV) chloride (SnCl_4) (11 mL, 94 mmol) is added by syringe and the solution is stirred for 30 min at -23°C (Note 10). At this time the brown solution is warmed to 23°C and stirring is continued for an additional 30 min. Saturated aqueous NH_4Cl (200 mL) is added and the mixture is concentrated under reduced pressure using a rotary evaporator to remove nitromethane. The resulting aqueous suspension is extracted with ethyl acetate (200 mL) and the organic extract is washed with brine (200 mL), dried over sodium sulfate (Na_2SO_4) and concentrated under reduced pressure using a rotary evaporator. The residue is subjected to flash chromatography on silica gel (250 g, 20 cm x 10 cm) using ethyl acetate:hexane (1:1) eluant (Note 7) to give 8.1 g (90%) of (2S,3S)-3-acetyl-8-carboethoxy-2,3-dimethyl-1-oxa-8-azaspiro[4.5]decane as a pale yellow oil (Notes 11 and 12).

2. Notes

1. Anhydrous tetrahydrofuran was prepared by distillation under argon from sodium benzophenone ketyl.

2. 2-Bromopropene, obtained from Aldrich Chemical Company, Inc., was distilled and then passed through a plug of activity IV basic alumina immediately before use.

3. The fine white emulsion formed at this stage was collected with the organic phase and was cleared in the subsequent brine washings.

4. This crude material was acceptable for use in the second step, although more p-toluenesulfonic acid will be required if large amounts of tributylamine are present. The diol mixture, free from tributylamine, can be obtained by careful chromatography on silica gel using ethyl acetate-hexane (1:1). The purified sample has the following characteristics: ^1H NMR (500 MHz, CDCl_3 , major isomer) δ : 1.10 (d, 3 H, $J = 6.5$, CH_3), 1.37 (s, 3 H, CH_3), 1.80 (s, 3 H, CH_3), 2.21 (br s, 2 H, 2 x OH), 3.77 (q, 1 H, $J = 5.6$, CH), 4.89 (d, 1 H, $J = 1.1$, $\text{CH}=\text{C}$), 5.06 (s, 1 H, $\text{CH}=\text{C}$); IR (film) cm^{-1} : 3421, 3397, 3390, 3364, 2981, 2937, 1088; MS (CI) m/z 113.0936 (113.0966 calcd for $\text{C}_7\text{H}_{14}\text{O}_2$, MH - H_2O).

5. The major isomer is assigned the 3R, 4S stereochemistry on the expectation that the addition would occur preferentially with Cram (Felkin-Ahn) selectivity.³ This assignment was confirmed by ^1H NMR DNOE experiments on the isobutyraldehyde acetal.

6. 1-Carboethoxy-4-piperidone was obtained from Aldrich Chemical Company, Inc., and used as received.

7. A series of 200-mL fractions was collected during flash chromatography. The product was eluted in fractions 3-8 as indicated by TLC analysis using 4% ethanolic phosphomolybdic acid stain.

8. This sample has the following characteristics: ^1H NMR (500 MHz, CDCl_3 , major isomer) δ : 1.17 (d, 3 H, $J = 5.1$, CH_3), 1.26 (t, 3 H, $J = 7.1$, OCH_2CH_3), 1.45 (s, 3 H, CH_3), 1.77 (s, 3 H, $\text{CH}_3\text{C}=\text{C}$), 1.60-1.81 (m, 5 H, 2 x CH_2 and CH), 3.43-3.75 (m, 4 H, 2 x CH_2N), 4.13 (q, 2 H, $J = 7.1$, OCH_2CH_3), 4.96 (s, 2 H, $\text{CH}_2=\text{C}$); IR (film) cm^{-1} : 2977, 1702, 1433, 1238, 1122; MS (CI) m/z 284.1850 (284.1861 calcd for $\text{C}_{15}\text{H}_{25}\text{NO}_4$, MH). Anal. Calcd for $\text{C}_{15}\text{H}_{25}\text{NO}_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.48; H, 8.90; N 4.89.

9. Nitromethane was dried by distillation of a 10:1 mixture of nitromethane and trifluoroacetic anhydride and collection of the center fraction that distilled at 100°C .

10. Tin(IV) chloride (SnCl_4) was obtained from Aldrich Chemical Company, Inc., and handled under an atmosphere of argon.

11. Gas chromatographic analysis using a 25-m 10% SP 2100 silicone column showed that this sample was 94% pure and contained one major unidentified impurity. Bulb-to-bulb distillation (200°C , 0.6 mm) of a 7.4-g sample of the crude product afforded 7.0 g (85%) of the product as a pale yellow oil, which was shown by GLC analysis to be of 100% purity. This sample has the following spectral characteristics: $[\alpha]_D -79.1^\circ$ (MeOH, c 1.0); ^1H NMR (500 MHz, CDCl_3) δ : 1.17 (d, 3 H, $J = 6.6$, CH_3), 1.25 (m, 6 H, OCH_2CH_3 and CH_3), 1.70-1.90 (m, 4 H, $2 \times \text{CH}_2$), 2.19 (s, 3 H, CH_3CO), 1.57 (d, 1 H, $J = 13.5$) 2.36 (d, 1 H, $J = 13.5$), 3.38-3.70 (m, 4 H, $2 \times \text{CH}_2\text{N}$), 3.89 (q, 1 H, $J = 6.6$, CH) 4.12 (q, 2 H, $J = 7.1$, OCH_2CH_3); ^{13}C NMR (125 MHz, CDCl_3) δ : 14.5, 15.6, 22.5, 28.3, 36.0, 37.0, 40.7, 41.1, 47.3, 58.4, 61.0, 79.1, 81.0, 155.5, 210.3; IR (film) cm^{-1} : 2977, 2937, 1705, 1701, 1698, 1472, 1455, 1434, 1365, 1356, 1274, 1237; MS (CI) m/z 284.1845 (284.1860 calcd for $\text{C}_{15}\text{H}_{25}\text{NO}_4$, MH). Anal. Calcd for $\text{C}_{15}\text{H}_{25}\text{NO}_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.38; H, 8.87; N, 4.88.

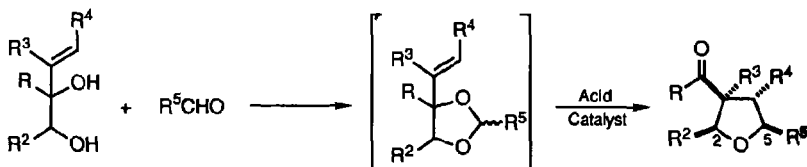
12. The enantiomeric excess of the product is >96%. This was determined by treating a sample of the ketone with sodium borohydride/methanol ($\text{NaBH}_4/\text{MeOH}$) (23°C) and separating the resulting 3:2 mixture of alcohol diastereomers by flash chromatography (silica gel, 2:3 ethyl acetate-hexane). The major alcohol diastereomer was converted to its Mosher ester⁴ [2.5 eq of (+)- α -methoxytrifluoromethylphenylacetic acid, 3 eq of dicyclohexylcarbodiimide, and 0.2 eq of 4-(dimethylamino)pyridine, CH_2Cl_2] and the crude esterification reaction mixture was analyzed using 500 MHz ^1H NMR. None of the minor diastereomer was observed while doping experiments established that 2% would have been detected [diagnostic signals: δ 1.80 (d, $J = 13.4$, major ester diastereomer); δ 1.82 (d, $J = 14.1$, minor ester diastereomer)].

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

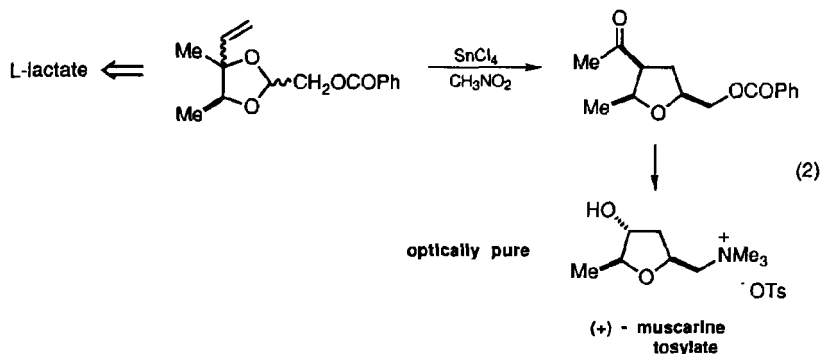
3. Discussion

This procedure illustrates a fundamentally new method for constructing substituted tetrahydrofurans.⁵⁻¹⁰ This practical method assembles the tetrahydrofuran ring from allylic diol and carbonyl components and in the process forms three ring bonds: C(2)-C(3), C(4)-C(5) and O-C(5). Both aldehydes (eq 1) and ketones (illustrated in the present procedure) can be employed as the carbonyl component. Although it is often convenient to isolate the acetal intermediate, conversion to the 3-acyltetrahydrofuran can also be accomplished in many cases by the direct reaction of the diol and carbonyl components.⁸ High *cis* stereoselectivity (at least 20:1) is observed in the preparation of tetrahydrofurans that contain single side chains at carbons 2 and 5 (eq 1). The kinetically controlled product also has the *cis* relationship of these side chains and the 3-acyl substituent.



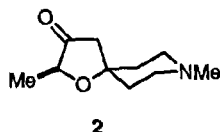
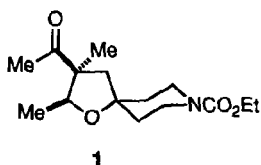
A definitive feature of this highly stereoselective new route to substituted tetrahydrofurans is that both *syn* and *anti* allylic diol stereoisomers typically afford identical tetrahydrofuran products. Thus, there is no need for stereoselective

construction of the allylic diol reaction partner. The construction of substituted tetrahydrofurans in high enantiomeric purity from non-racemic allylic diol precursors has also been established.^{5,7} The rearrangement illustrated in eq 2 is the key step in a recent synthesis of (+)-muscarine.



The scope and mechanism of the SnCl_4 -promoted rearrangement of allylic acetals have been investigated in detail and these studies provide considerable guidance for using this new tetrahydrofuran synthesis.⁵⁻¹⁰ Three major limitations emerge from studies conducted to date: (1) When the tetrahydrofuran construction involves a ketone, and thus forms a quaternary center at C(5), allylic diols with alkene substituents more nucleophilic than terminal vinyl rearrange in highest yield. (2) Allylic acetals that are reluctant to ring open in the presence of acid catalysts to generate oxocarbenium ions often undergo decomposition, rather than conversion to acyltetrahydrofuran products. (3) Allylic acetals that form highly stabilized oxocarbeniums (e.g., cinnamaldehyde-derived acetals) do not undergo conversion to 3-acyltetrahydrofurans.

This procedure illustrates the asymmetric synthesis of a spirobicyclic tetrahydrofuran from the reaction of readily available (S)-3-[[{(1,1-dimethylethyl)diphenylsilyl}oxy]-2-butanone² with cyclic ketones.¹⁰ The specific example described here affords an azaspirobicyclic tetrahydrofuran **1** that is structurally related to a recently reported class of powerful muscarinic agonists, exemplified by **2**.¹¹ Consistent with limitation (1) noted above, the related reaction of 3-methyl-4-pentene-2,3-diol (which contains a less-nucleophilic terminal vinyl participant) occurs in lower yield. As with other acetals that contain an electron-withdrawing heteroatom β or γ to the acetal carbon, the rearrangement described in this procedure is more efficient in nitromethane than in the less-ionizing solvent dichloromethane (CH_2Cl_2).⁷



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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2-Bromopene: Propene, 2-bromo- (8); 1-Propene, 2-bromo- (9); (557-93-7)

tert-Butyllithium: Lithium, *tert*-butyl- (8); Lithium, (1,1-dimethylethyl)- (19); (594-19-4)

3-(S)-[(*tert*-Butyldiphenylsilyl)oxy]-2-butanone: 2-Butanone, 3-[(1,1-dimethylethyl)-diphenylsilyl]oxy-, (S)- (12); (135367-18-9)

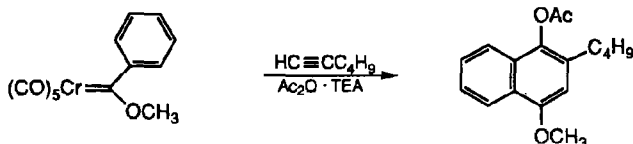
Tetrabutylammonium fluoride: Ammonium, tetrabutyl-, fluoride (8); 1-Butanaminium, N,N,N-tributyl-, fluoride (9); (429-41-4)

1-Carboxy-4-piperidone: 1-Piperidinecarboxylic acid, 4-oxo-, ethyl ester (8,9); (29976-53-2)

p-Toluenesulfonic acid monohydrate (8); Benzenesulfonic acid, 4-methyl-, monohydrate (9); (6192-52-5)

Nitromethane: Methane, nitro- (8,9); (75-52-5)

**SYNTHESIS OF 2-SUBSTITUTED NAPHTHALENEDIOL
DERIVATIVES USING CHROMIUM CARBENE COMPLEXES:
1-ACETOXY-2-BUTYL-4-METHOXYNAPHTHALENE
(1-Naphthalenol, 2-butyl-4-methoxy-, acetate)**



Submitted by Joseph M. Timko and Ayako Yamashita.¹

Checked by Paul A. Johnson and Albert I. Meyers.

1. Procedure

Caution! All operations should be conducted in a well-ventilated hood with breathing protection. The chromium carbene complex generally is contaminated with the very volatile and toxic chromium hexacarbonyl, which is also generated as a by-product of the reaction.

An oven-dried, 2-L, three-necked, round-bottomed flask, equipped with a nitrogen inlet, magnetic stirring bar, thermometer, and reflux condenser, under an inert nitrogen atmosphere (Note 1), is charged with 1.22 g (10 mmol) of 4-dimethylaminopyridine (Note 2), 500 mL of tetrahydrofuran (Note 3), 11.0 mL (95.7 mmol) of 1-hexyne (Note 4), 13.2 mL (140 mmol) of acetic anhydride (Note 5), 9.8 mL (70 mmol) of triethylamine (Note 2), 20.0 g (64.0 mmol) of penta-carbonyl[phenyl(methoxy)chromium]carbene (Notes 1 and 6), and a final 100-mL rinse of tetrahydrofuran. The solution is heated to reflux with an oil bath and heating is

maintained until TLC indicates that the chromium complex is totally consumed (about 45-60 min, Note 7). The solution is then cooled to ambient temperature, 30 g of silica gel is added (Note 8), and volatile organic material is removed under reduced pressure (rotary evaporator). The green solids are transferred to a filter funnel and washed with hexane until TLC indicates that all products have been removed (5 x 100 mL) (Note 9). The hexane filtrate is then concentrated under reduced pressure to give crude product contaminated with chromium hexacarbonyl. To the mixture is added 20 mL of isopropyl alcohol and the insoluble chromium hexacarbonyl is removed by filtration (Note 9). The filtrate is concentrated under reduced pressure to give 14.0 g of crude product which is purified by silica gel chromatography (Note 10). Appropriate fractions are combined and the solvent is removed under reduced pressure to give 1-acetoxy-2-butyl-4-methoxynaphthalene (11.8 g, >95% pure based on HPLC, 68% yield based on the carbene complex, Notes 6 and 11) as a light yellow oil which crystallizes on standing (Note 12). If desired, the product can be crystallized from isopropyl alcohol (2.5 mL/g) to give white crystals, mp 49-50°C (>99% pure based on HPLC).

2. Notes

1. Although slowly decomposed by exposure to air (oxygen), the chromium carbene complex is sufficiently stable to handle using ordinary nitrogen drybox techniques. The complex should be stored at refrigerator temperature. All solvents and liquid reagents were routinely deoxygenated prior to use with a slow stream of nitrogen.

2. 4-Dimethylaminopyridine and triethylamine were obtained from the Aldrich Chemical Company, Inc., and used without further purification. If 4-dimethylaminopyridine is omitted, the level of impurities rises.²

3. Tetrahydrofuran, UV grade, was obtained from Burdick and Jackson or Mallinkrodt Inc. and used after distillation from calcium hydride.

4. 1-Hexyne was obtained from Farchan Chemical Company or Aldrich Chemical Company, Inc., and used without further purification.

5. Acetic anhydride was obtained from Mallinkrodt Inc. or Aldrich Chemical Company, Inc., and used without further purification.

6. Pentacarbonyl[phenyl(methoxy)carbene]chromium was prepared by the checkers in 75% yield according to the literature: Hegedus, L. S.; McGuire, M. A.; Schultze, L. M. *Org. Synth.* **1987**, *65*, 140. This material was stored under nitrogen at -30°C and purified immediately prior to use by filtration through a plug of Celite (hexane solvent). If the chromium carbene is purchased from Aldrich Chemical Company, Inc., the submitters found it was only 65% pure based on capillary GLC analysis.

7. Analytical thin layer chromatography (TLC) was conducted on 10 x 2.5-cm precoated glass plates (silica gel GF, 0.25-mm thickness, Analtech), eluted with 10% ethyl acetate in hexane, and visualized with both UV (254 nm) and aqueous 50% sulfuric acid spray/heating. The carbene complex moves as an orange spot on TLC; the reaction is complete when this spot is no longer visible.

8. The chromium complex degrades into chromium hexacarbonyl and an intractable green chromium tar. The addition of silica gel prior to solvent removal adsorbs this material before it can form a tar.

9. The solid material containing chromium waste was placed in a container for heavy metal wastes and disposed of by a commercial service according to approved procedures

10. Silica gel (obtained from E. Merck or Alfa Products, Morton/Thiokol Inc.) was used (420 g, 70-230 mesh) in a 5.5 x 60-cm column eluted with 10% ethyl acetate in hexane.

11. This reaction has been performed on a scale up to a 20 times larger by the submitters (400 g of chromium carbene complex) with identical results.

12. The NMR spectrum was as follows: ^{13}C NMR (75 MHz, CDCl_3) δ : 17.3, 20.2, 23.1, 31.4, 67.4, 127.1, 127.2, 127.9, 128.2, 128.3, 128.6, 128.7, 130.1, 130.3, 141.2, 172.0, 216.1.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

The regioselective preparation of 2-substituted naphthalenediol derivatives having the diols differentially protected in a predictable and straightforward manner, previously not directly attainable, is readily accomplished using chromium carbene complexes. First prepared by E. O. Fischer, chromium carbene complexes react readily with alkynes (extensively investigated by K. H. Dötz, and others).³ Steric effects dictate the substitution pattern observed^{2,4} and the reaction mechanism has been widely studied.²

The title compound (U-66,858) and analogues are of interest as lipoxygenase inhibitors with potential application to the treatment of asthma and related disorders.

1. The Upjohn Company, Kalamazoo, MI 49001.
2. Yamashita, A.; Timko, J. M.; Watt, W. *Tetrahedron Lett.* **1988**, *29*, 2513, and references therein.
3. For a recent review, see Dötz, K. H. *Pure Appl. Chem.* **1983**, *55*, 1689.
4. Wulff, W. D.; Tang, P.-C.; McCalum, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 7677; Wulff, W. D.; Chan, K.-S.; Tang, P.-C.; *J. Org. Chem.* **1984**, *49*, 2293; Yamashita, A.; Toy, A. *Tetrahedron Lett.* **1986**, *27*, 3471; and references therein.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1-Acetoxy-2-butyl-4-methoxynaphthalene: 1-Naphthalenol, 2-butyl-4-methoxy-, acetate (11); (99107-52-5)

4-Dimethylaminopyridine: Pyridine, 4-(dimethylamino)- (8); 4-Pyridinamine, N,N-dimethyl- (9); (1122-58-3)

1-Hexyne (8,9); (693-02-7)

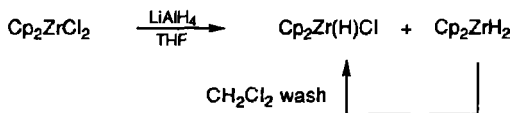
Acetic anhydride (8); Acetic acid anhydride (9); (108-24-7)

Triethylamine (8); Ethanamine, N,N-diethyl- (9); (121-44-8)

Pentacarbonyl[phenyl(methoxy)chromium]carbene: Chromium, pentacarbonyl(α -methoxybenzylidene)- (8); Chromium, pentacarbonyl(methoxyphenylmethylene)-, (OC-6-21) (9); (27436-93-7)

SCHWARTZ'S REAGENT

(Zirconium, chlorobis(η⁵-2,4-cyclopentadien-1-yl)hydro-)



Submitted by Stephen L. Buchwald,¹ Susan J. LaMaire, Ralph B. Nielsen,

Brett T. Watson, and Susan M. King.

Checked by Daniel J. Keavy and Robert K. Boeckman, Jr.

1. Procedure

Caution! The washing procedure described in Note 8 should be followed carefully. On one occasion, allowing a contact time of ca. 1 hr while attempting to use a cannula filter to remove the methylene chloride led to an exothermic decomposition reaction.

To a dry, 1-L Schlenk flask equipped with a magnetic stirring bar is added under argon zirconocene dichloride (100 g, 0.342 mol) (Note 1), followed by dry tetrahydrofuran (650 mL) (Note 2). Dissolution of the solid is accomplished by gentle heating with a heat gun. To the solution at ~35°C (Note 3) is added dropwise, over a 45-min period, a filtered solution (Notes 4,5) of lithium aluminum hydride (3.6 g, 94 mmol) (Note 4) in ethyl ether (100 mL) (Note 6,7). The resulting suspension is stirred at room temperature for 90 min. The mixture is then Schlenk-filtered (Figure 1) under argon using a "D" frit. The resulting white solid is washed with tetrahydrofuran (4 x 75 mL), methylene chloride (2 x 100 mL) (Note 8) with stirring or agitation of the stirbar immersed in the slurry, and then with ether (4 x 50 mL). The resulting white solid is

dried under reduced pressure to give a white powder (Note 9), 66 g, 75% yield (Note 10).

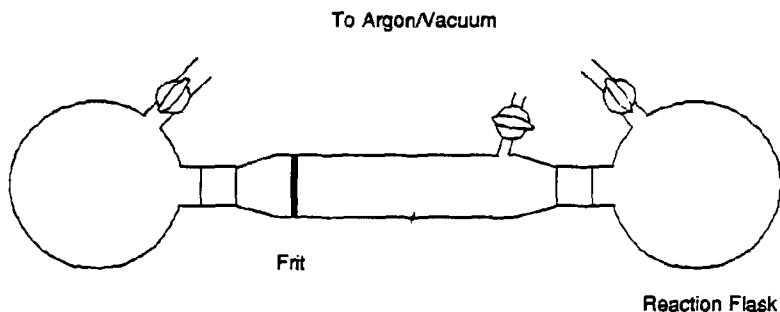
2. Notes

1. Zirconocene dichloride is purchased from Boulder Scientific Co., and used without any further purification.

2. Tetrahydrofuran is distilled from sodium/benzophenone ketyl under argon at atmospheric pressure immediately before use.

3. Crystallization occurs if the temperature is allowed to fall below $\sim 35^{\circ}\text{C}$. The reaction can be conducted successfully even if a small amount of solid forms.

Figure 1



4. This solution is prepared by adding lithium aluminum hydride to ethyl ether, stirring the suspension for 10 min, and allowing the undissolved material to settle to the bottom of the flask. The clear solution is then filtered under argon using a modified cannula (Figure 2) fitted with a piece of glass fiber filter (Number 34 Glass, 24 mm,

purchased from Schleicher & Schuell); a Schlenk-filtered or commercial clear solution would work as well.

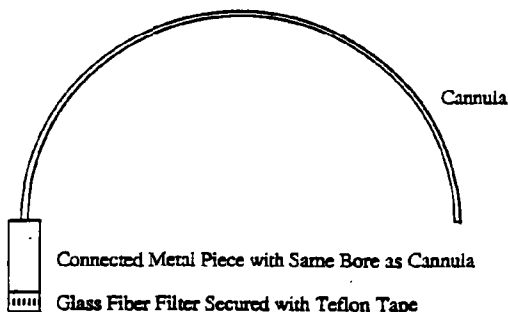
5. Lithium aluminum hydride (95%) is purchased from Alfa Products, Morton/Thiokol, Inc.

6. A slightly exothermic reaction results that maintains the temperature of the reaction mixture at $\sim 35^{\circ}\text{C}$ during the addition.

7. Ethyl ether is distilled from sodium/benzophenone ketyl under argon at atmospheric pressure immediately before use.

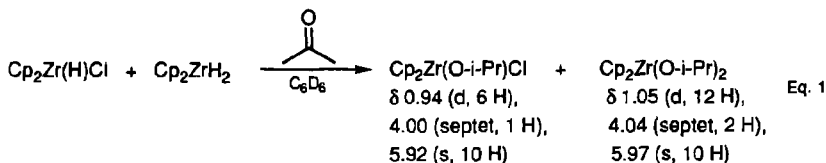
8. Methylene chloride is distilled from calcium hydride under argon at atmospheric pressure immediately before use. It is important to keep the methylene chloride wash in contact with the Schwartz's Reagent for a maximum period of 10 min; use of a frit filter is essential.

Figure 2



9. Schwartz's Reagent is an air, moisture, and moderately light sensitive compound that should be dried in the dark, and protected from moisture and light during storage.

10. A small sample of the hydride is suspended in benzene-d₆ and assayed in a 5-mm NMR tube by treatment with a known amount of excess acetone (Equation 1). The relative areas of the signal for the mono- and disopropoxides are determined by ¹H NMR (300 MHz, C₆D₆ integrating the methyl doublets): Cp₂Zr(H)Cl: 94-96%, Cp₂ZrH₂: 4-6%.^{2a}



Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

Schwartz's Reagent³ is available commercially (from the Aldrich Chemical Company, Inc.) although it is quite expensive. Two literature preparations of this important reagent are available. The first utilizes LiAl(OtBu)₃H to reduce zirconocene dichloride.⁴ The second method utilizes sodium bis(2-methoxyethoxy) aluminum hydride (RED-AL) as the reducing agent.^{2a} The disadvantages of these procedures have been discussed.³

Wailes, in his original report on the preparation of $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ investigated the lithium aluminum hydride reduction of zirconocene dichloride and found that this leads to considerable overreduction to give Cp_2ZrH_2 .⁴ Later it was found that treatment of Cp_2ZrH_2 with methylene chloride converts the dihydride into Schwartz's Reagent.³

In the procedure described here, zirconocene dichloride is reduced to a mixture of $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$, and Cp_2ZrH_2 using a solution of lithium aluminum hydride. Washing the mixture with methylene chloride converts the Cp_2ZrH_2 into the desired $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$. This method circumvents the need for expensive reducing agents and the use of the filtered lithium aluminum hydride solution substantially simplifies the product isolation. The procedure can be performed in 3-4 hr and does not require the use of a glove box thus making it an experimentally simple, inexpensive preparation for large scale batches of Schwartz's Reagent.

The utility of Cp_2ZrHCl for hydrozirconation was discovered by Schwartz.² Many subsequent applications of this useful reagent have been documented.⁵ One such application is illustrated in the conjugate addition of a vinylzirconium reagent to form 3-(1-octen-1-yl)cyclopentanone which is detailed in the following procedure.⁶ In some cases Schwartz's Reagent (or its equivalent) can be prepared and used in situ.⁷

1. Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139.
2. (a) Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1979**, *101*, 3521; (b) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115; (c) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333; (d) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679; (e) Bertelo, C. A.; Schwartz, J. *J. Am. Chem. Soc.* **1976**, *98*, 262.
3. Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Tetrahedron Lett.* **1987**, *28*, 3895.

4. (a) Wailes, P. C.; Weigold, H. *J. Organomet. Chem.* **1970**, *24*, 405; (b) Wailes, P. C.; Weigold, H. *Inorg. Synth.* **1979**, *19*, 223.
5. Negishi, E.-i.; Takahashi, T. *Aldrichimica Acta* **1985**, *18*, 31 and references therein.
6. Chu Sun, R.; Okabe, M.; Coffen, D. L.; Schwartz, J. *Org. Synth.* **1992**, *71*, 83.
7. Negishi, E.-i.; Miller, J. A.; Yoshida, T. *Tetrahedron Lett.* **1984**, *25*, 3407.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

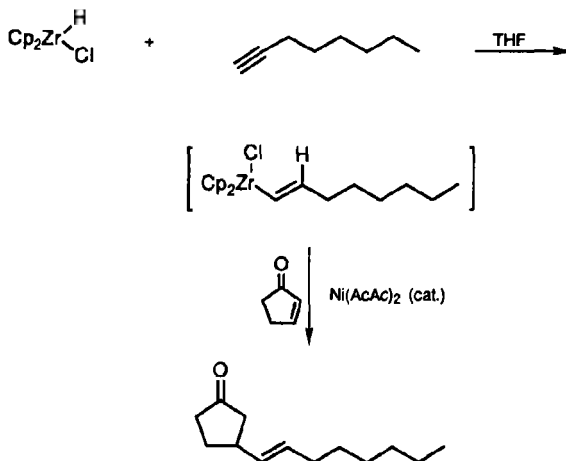
Schwartz's Reagent: Bis(cyclopentadienyl)zirconium chloride hydride: Zirconium, chlorodi- π -cyclopentadienylhydro- (8); Zirconium, chlorobis(η^5 -2,4-cyclopentadien-1-yl)hydro- (9); (37342-97-5)

Zirconocene dichloride: Zirconium, dichloro- π -cyclopentadienyl- (8)-; Zirconium, dichlorobis(η^5 -2,4-cyclopentadien-1-yl)- (9); (1291-32-3)

CONJUGATE ADDITION OF A VINYLZIRCONIUM REAGENT:

3-(1-OCTEN-1-YL)CYCLOPENTANONE

(Cyclopentanone, 3-(1-octenyl)-, (E)-)



Submitted by Ruen Chu Sun,¹ Masami Okabe,¹ David L. Coffen,¹
and Jeffrey Schwartz.²

Checked by Daniel J. Keavy and Robert K. Boeckman, Jr.

1. Procedure

3-(1-Octen-1-yl)cyclopentanone.³ A 38.7-g quantity (0.150 mol) of chlorobis(η^5 -cyclopentadienyl)hydrido-zirconium, Schwartz's reagent, (Note 1) is weighed into an oven-dried, 250-mL, three-necked flask. The flask equipped with argon inlet and exit tubes, a thermometer and magnetic stirrer is placed in an ice/water cooling bath.

Under an atmosphere of argon, 50 mL of dry tetrahydrofuran (Note 2) and 23.6 mL (0.16 mol) of freshly distilled 1-octyne (Note 3) are added. The ice/water cooling bath is used to keep the temperature between 15°C and 25°C during the addition. Stirring is continued in the ice bath for 2 hr to control a mildly exothermic reaction; then the flask is wrapped in aluminum foil and stirred overnight at room temperature (elapsed time is 18 hr). At this point, 10.9 mL (0.130 mol) of freshly distilled 2-cyclopentenone (Note 3) is added and the reaction mixture is chilled in an ice bath for 10 min. To the cooled reaction mixture a total of 3.34 g (0.0130 mol) of vacuum-sublimed (at 180°C), powdered, solid nickel acetylacetonate (Notes 3,4) is added in three portions at 10-min intervals, keeping the temperature of the reaction mixture below 50°C (Notes 5,6).

The mixture is stirred for 2 hr in the ice bath and for 2 hr at room temperature, then poured into a large Erlenmeyer flask containing 150 mL of 1 N hydrochloric acid and 200 mL of ice/water mixture. Hexane (400 mL) is added and the quenched reaction mixture is stirred for 30 min. Solid material is removed by vacuum filtration (Note 7) and the solids are washed with hexane (3 x 70 mL). The combined filtrates are transferred to a separatory funnel and the organic layer is removed. The aqueous layer (Note 7) is extracted with 300 mL of hexane and the extract is combined with the original organic layer. After the organic layer is washed successively with 300-mL portions of saturated sodium bicarbonate solution and brine, it is dried over sodium sulfate and concentrated under reduced pressure to give 24.8 g of crude product. The crude product is placed on a chromatography column prepared from 550 g of silica gel and hexane. The column is eluted with 2% ethyl acetate in hexane until 3.5 L of eluant has been collected. Then 4% ethyl acetate in hexane is used. The fractions containing the product (TLC) are combined and evaporated, finally under high vacuum, to afford 15.4 g (61%) of a very pale yellow liquid (Note 8). GC analysis of this product on an OV17 50-m capillary column (100°C to 200°C at 5°C/min) shows it to be 98.2% pure.

The material is distilled in a Kugelrohr apparatus at 0.15 mm and an oven temperature of 95-105°C to give 15.0 g (59% overall yield) of material with GC purity of 98.3% (Note 9).

2. Notes

1. Chlorobis(η^5 -cyclopentadienyl)hydrido­zirconium was prepared by lithium aluminum hydride reduction of the dichloro compound using the procedure of Buchwald and co-workers.⁴ When carried out using chlorobis(η^5 -cyclopentadienyl)-hydrido­zirconium obtained from a commercial source, the procedure afforded only a 28% yield of final product.

2. Tetrahydrofuran was distilled from sodium/benzophenone before use.

3. 1-Octyne, cyclopentenone, and nickel acetylacetonate were purchased from the Aldrich Chemical Company, Inc. The checkers recrystallized the latter compound from anhydrous methanol followed by azeotropic drying with hot toluene.

4. For some applications of this chemistry, it may be preferable first to reduce the nickel catalyst with DIBAL.³

5. The checkers observed a significant induction period prior to onset of the exothermic reaction. Care must be taken to avoid addition of the nickel acetylacetonate too rapidly initially or temperature control becomes difficult.

6. In several separate small scale experiments, it was noted that the coupling reaction was not impeded by adding pyridine, triethylamine, t-butyl alcohol, chlorotrimethylsilane, or diisopropylamine to the reaction mixture before adding the nickel catalyst. These results suggest that a variety of functional groups can be present in the enone partner of the coupling reaction. In addition toluene can be used instead of tetrahydrofuran as the solvent.

7. Disposal of waste materials containing nickel salts should be carried out in an environmentally acceptable manner.

8. The checkers employed a flash chromatography technique, and 4% ethyl acetate/hexanes as the TLC solvent system to monitor the chromatographic separation.

9. The NMR spectrum of the product [^1H NMR (CDCl_3) δ] showed a characteristic set of multiplets from 0.8 to 2.9 ppm and olefinic protons at 5.43 (dd, 1 H, $J = 15.4$ and 6.4) and 5.49 ppm (dt, 1 H, $J = 15.4$ and 5.8); ^{13}C NMR (75 MHz, CDCl_3) δ : 14.0, 22.6, 28.7, 29.3, 29.9, 31.6, 32.4, 38.1, 39.7, 44.9, 130.6, 131.9, 219.0; IR (neat) cm^{-1} : 1743; mass spectrum m/e 194 (M^+). Anal. Calcd for $\text{C}_{13}\text{H}_{22}\text{O}$: C, 80.35; H, 11.41. Found: C, 80.40; H, 11.35. The checkers employed a 30-m Durawax DX3 column for the GC analysis and found a purity of 97%.

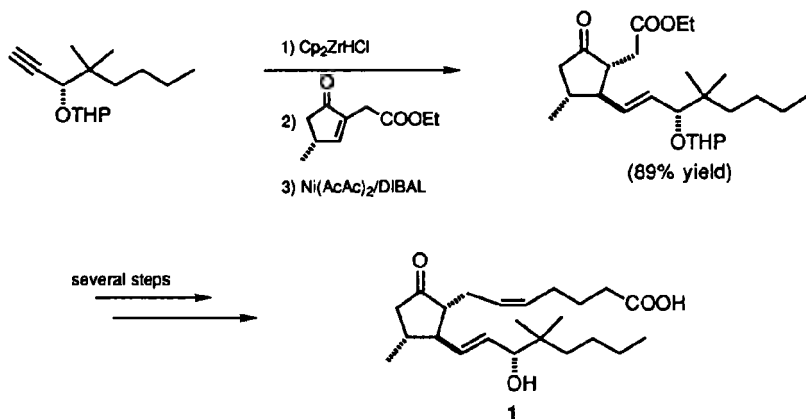
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

This example does not illustrate the highest yield application of this chemistry. Coupling of 1-octyne and cyclopentenone was selected because these materials are commercially available and because this coupling exemplifies, in a prototypical fashion, the application of this powerful chemistry to prostaglandin synthesis. Several additional examples are presented in the original publication.³

A closely related coupling reaction is a key step in a synthesis of the anti-ulcer prostaglandin **1**, a synthesis that was developed for large scale preparation of this compound.⁵



The simplicity of operation and flawless rendering of (E)-geometry make this an attractive alternative to vinylcuprate additions.

1. Chemistry Research Department, Hoffmann-La Roche Inc., Nutley, NJ 07110.
2. Department of Chemistry, Princeton University, Princeton, NJ 08544.
3. Schwartz, J.; Loots, M. J.; Kosugi, H. *J. Am. Chem. Soc.* **1980**, *102*, 1333.
4. Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Tetrahedron Lett.* **1987**, *28*, 3895; *Org. Synth.* **1992**, *71*, 77.
5. Coffen, D. L.; Manchand, P. S.; Truesdale, L. K.; Eur. Pat. Appl. Ep 153 689, 1985 (to Hoffmann-La Roche & Co.); *Chem. Abstr.* **1986**, *104*, 186231v.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

3-(1-Octen-1-yl)cyclopentanone: Cyclopentanone, 3-(1-octenyl)-, (E)- (10);
 (64955-00-6)

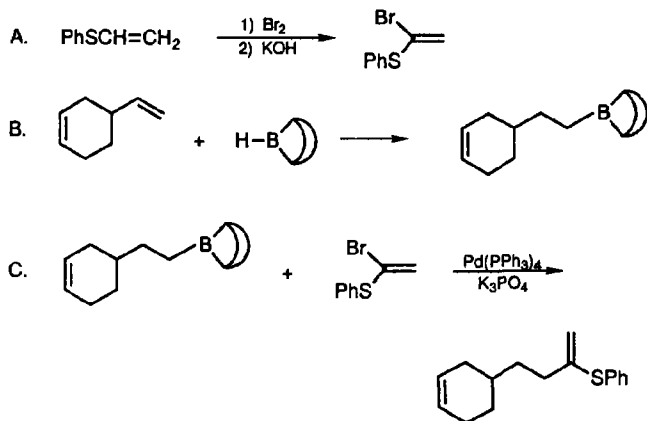
Chlorobis(η^5 -cyclopentadienyl)hydrido­zirconium: Zirconium, chlorodi- π -
 cyclopentadienylhydro- (8); Zirconium, chlorobis(η^5 -2,4-cyclopentadien-1-yl)hydro-
 (9); (37342-97-5)

1-Octyne (8,9); (629-05-0)

2-Cyclopentenone: 2-Cyclopenten-1-one (8,9); (930-30-3)

Nickel acetylacetonate: Nickel, bis(2,4-pentanedionato- (8); Nickel, bis(2,4-
 pentanedionato-O,O')-, (SP-4-1)- (9); (3264-82-2)

PALLADIUM(0)-CATALYZED REACTION OF 9-ALKYL-9-BORABICYCLO[3.3.1]NONANE WITH 1-BROMO-1-PHENYLTHIOETHENE:
4-(3-CYCLOHEXYL)-2-PHENYLTHIO-1-BUTENE



Submitted by Tatsuo Ishiyama, Norio Miyaura, and Akira Suzuki.¹

Checked by Ron J. Graham and Leo A. Paquette.

1. Procedure

A. 1-Bromo-1-phenylthioethene. A 300-mL, two-necked, round-bottomed flask is fitted with a magnetic stirring bar, pressure-equalizing dropping funnel, and a reflux condenser to which a nitrogen inlet tube and an oil bubbler are attached, and flushed with nitrogen (Note 1). In the flask are placed 13.6 g (100 mmol) of phenyl vinyl sulfide (Note 2) and 80 mL of ether (Note 3), which are then cooled to ca. -78°C with a dry ice-methanol bath. Bromine (16.0 g, 100 mmol) is added dropwise over 30 min to the

stirred solution. After the solution is warmed to room temperature, 40 mL of absolute ethanol, followed by a solution of 8.0 g (140 mmol) of potassium hydroxide in 80 mL of absolute ethanol is added dropwise to the resulting slightly red solution over 30 min. The light brown solution containing a white precipitate of potassium bromide is stirred at room temperature for 2 hr. The precipitate is removed by filtration and the filtrate is concentrated by rotary evaporation. The residue is treated with 200 mL of ether and 200 mL of water. The organic layer is separated, washed with brine (50 mL), and dried over anhydrous magnesium sulfate. After rotary evaporation of the solvent, the residual oil is distilled under reduced pressure to give 17.2 g (80% yield) of 1-bromo-1-phenylthioethene (Note 4) as a colorless liquid, bp 49-50°C (0.07 mm).

B. *9-[2-(3-Cyclohexenyl)ethyl]-9-BBN*. A 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, thermometer, reflux condenser, and a pressure-equalizing addition funnel capped with a rubber septum. The apparatus is connected through the condenser to a nitrogen source and an oil bubbler and flushed with nitrogen. The flask is charged with 35 mL of tetrahydrofuran (Note 5) and 8.32 g (77.0 mmol) of 4-vinyl-1-cyclohexene (Note 6) and cooled to 0°C. A 0.5 M solution of 9-BBN (9-borabicyclo[3.3.1]nonane) in tetrahydrofuran (154 mL, 77.0 mmol) (Note 7) is transferred via cannula to the addition funnel and is added dropwise with stirring over 1 hr maintaining the temperature at 0-5°C. The reaction mixture is stirred for 1 hr at 0°C and for 1.5 hr at room temperature. The solution obtained is used in the next step without further treatment (Note 8).

C. *4-(3-Cyclohexenyl)-2-phenylthio-1-butene*. To the above solution of the borane derivative, 0.809 g (0.700 mmol) of tetrakis(triphenylphosphine)palladium(0) (Note 9), 1.47 g (5.60 mmol) of triphenylphosphine (Note 10), 35 mL of 3 M potassium phosphate in water (Note 11), and finally 15.1 g (70.0 mmol) of 1-bromo-1-phenylthioethene are added and the resulting mixture is heated at reflux for 3 hr with stirring. The light brown solution is cooled to room temperature and treated with 6.4 g

(100 mmol) of ethanolamine (Note 12) for 1 hr. Then 100 mL of hexane and 100 mL of water are added. The organic layer is separated, washed with 100 mL of water, and dried over anhydrous magnesium sulfate. The drying agent is removed by filtration and the filtrate is concentrated by rotary evaporation. The addition of 250 mL of hexane to the residual viscous oil, containing some solid, precipitates the 9-BBN/ethanolamine complex. The solid is removed by filtration and is washed with hexane (50 mL x 3), and the filtrate is concentrated using a rotary evaporator. The crude product is passed through a short silica gel column (60-200 mesh, 60 g) using hexane as an eluent (Note 13). After removal of the hexane, the residue is distilled under reduced pressure to give 12.5-13.9 g (73-81%) of 4-(3-cyclohexenyl)-2-phenylthio-1-butene as a colorless liquid, bp 114-116°C (0.04 mm) (Note 14).

2. Notes

1. All glassware was pre-dried in an oven at 120°C for 2 hr, assembled while hot, and allowed to cool under a stream of nitrogen.

2. The preparation of phenyl vinyl sulfide is described *Org. Synth., Coll. Vol. VII* 1990, 453. The compound is also available from Aldrich Chemical Company, Inc.

3. Ether was distilled from benzophenone ketyl under nitrogen before use.

4. The product is labile at room temperature and should be stored in a freezer. Spectral data are as follows: IR (neat) cm^{-1} : 3076, 3060, 1583, 1477, 1440, 1069, 752, 689; ^1H NMR (300 MHz, CDCl_3) δ : 5.73 (d, 1 H, $J = 2.3$), 5.83 (d, 1 H, $J = 2.3$), 7.23-7.46 (m, 5 H).

5. Tetrahydrofuran is distilled from benzophenone ketyl under nitrogen before use.

6. 4-Vinyl-1-cyclohexene was obtained from Aldrich Chemical Company, Inc., and distilled it prior to use.

7. A 0.5 M solution of 9-BBN in tetrahydrofuran was purchased from Aldrich Chemical Company, Inc., and was used without additional purification. The preparation² of the reagent by hydroboration of 1,5-cyclooctadiene with borane/tetrahydrofuran complex is reported.

8. If necessary, 9-[2-(3-cyclohexenyl)ethyl]-9-BBN³ can be purified by removal of the solvent and vacuum distillation under nitrogen [bp 103°C (0.035 mm)].

9. The preparation of tetrakis(triphenylphosphine)palladium(0) is described.⁴ It is also available from Aldrich Chemical Company, Inc.

10. Triphenylphosphine was obtained from Nakarai Chemicals, Japan. When the reaction is carried out without additional triphenylphosphine, the yield of coupling product may drop to 60-70% and the product is accompanied by the by-products, phenyl vinyl sulfide and 4-vinyl-1-cyclohexene, derived from β -hydride elimination.

11. The solution is prepared by dissolving 22.3 g (105 mmol) of potassium phosphate (Nakarai Chemicals, Japan) in water and adjusting the final volume to 35 mL. The original method⁵ used sodium hydroxide as base; potassium phosphate is desirable for the extension of the present procedure to base-sensitive compounds. Under such conditions, the reaction with 9-(10-carbomethoxydecanyl)-9-BBN proceeds similarly without saponification of the ester group.

12. Ethanolamine was purchased from Nakarai Chemicals, Japan. The reagent reacts with the resulting 9-BBN residue to give an air stable 1:1 adduct⁶ that is insoluble in hexane.

13. This operation effectively removes the remaining palladium-containing compounds, phosphine derivatives, and borane residues.

14. Gas chromatographic analysis of the product (Finnigan ITD 800-fused silica capillary, SE 30 column, 0.35 mm x 25 m, column temperature 80-250°C, injection temperature 250°C) shows that the chemical purity is 94-98.5%. The spectral data are as follows: IR (neat) cm^{-1} : 3030, 2920, 1615, 1590, 1480, 1440, 750, 690; ¹H NMR

(300 MHz, CDCl_3) δ : 1.00-1.90 (m, 6 H), 1.90-2.20 (m, 3 H), 2.20-2.50 (m, 2 H), 4.88 (s, 1 H), 5.15 (s, 1 H), 5.64 (s, 2 H), 7.20-7.50 (m, 5 H).

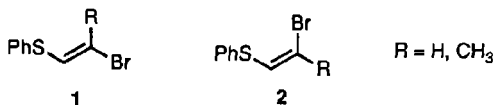
The product deteriorates at room temperature and should be stored in the freezer.

Waste Disposal Information

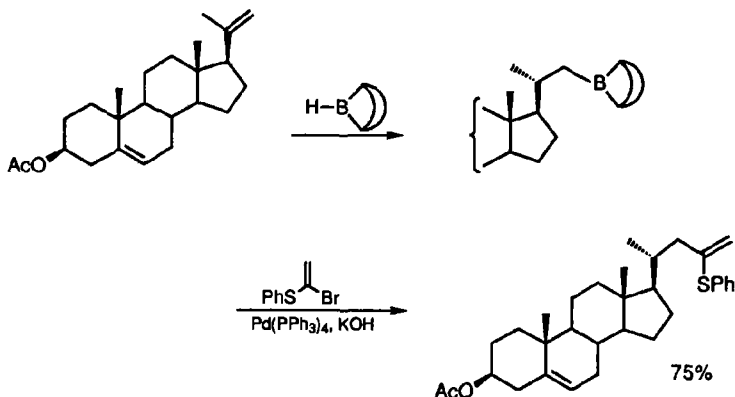
All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

The reaction described here is an attractive method for the synthesis of alkenyl sulfides via the cross-coupling reaction⁵ of 9-alkyl-9-BBN with bromo(phenylthio)ethenes induced by a palladium catalyst. Bromo(phenylthio)ethene has several advantages in terms of its practical use for the cross-coupling reaction. Coupling occurs at the bromine position, but no coupling at the sulfur position is obtained under conditions using an excess of 9-alkyl-9-BBN. Thus, the formation of dialkylation products is completely avoided. The reaction is highly stereoselective and is readily extended to the coupling with (E)- and (Z)-2-bromo-1-phenylthio-1-alkene derivatives (1 and 2)⁷ to afford stereodefined vinylic sulfides. The generality of the



present method was demonstrated by the stereoselective hydroboration of a side chain of a steroid, followed by the cross-coupling reaction.



The reactions⁸ of (E)- or (Z)-1-alkenyl or 1,3-alkadienylboronic esters with **1** or **2** provide simple routes for stereoselective syntheses of 1,3-alkadienyl and 1,3,5-alkatrienyl phenyl sulfides.

Not only boron derivatives, but also Grignard reagents⁹ are reported to undergo a related coupling reaction with bromo(phenylthio)ethene derivatives. Other methods reported for the synthesis of alkenyl sulfides are condensation of carbonyl compounds with 1-methylthioalkylphosphonate esters¹⁰ or alkylthiomethyl(trimethyl)silane,¹¹ addition¹² of organothioalkoxides to alkynes, reduction¹³ of 1-alkynyl sulfides with metal hydride reagents, and substitution¹⁴ of 1-bromo-1-alkenes with sulfur reagents. However, most of these methods may lead to a mixture of geometrical isomers, the separation of which is difficult.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

1-Bromo-1-phenylthioethene; Benzene, [(2-bromoethenyl)thio]- (9); (35088-66-5)

Phenyl vinyl sulfide: Sulfide, phenyl vinyl (8); Benzene, (ethenylthio)- (9); (1822-73-7)

Bromine (8,9); (7726-95-6)

9-[2-(3-Cyclohexenyl)ethyl]-9-BBN: 9-Borabicyclo[3.3.1]nonane,

9-[2-(3-cyclohexen-1-yl)ethyl]- (10); (69503-86-2)

4-Vinyl-1-cyclohexene: Cyclohexene, 4-vinyl- (8); Cyclohexene,

4-ethenyl- (9); (100-40-3)

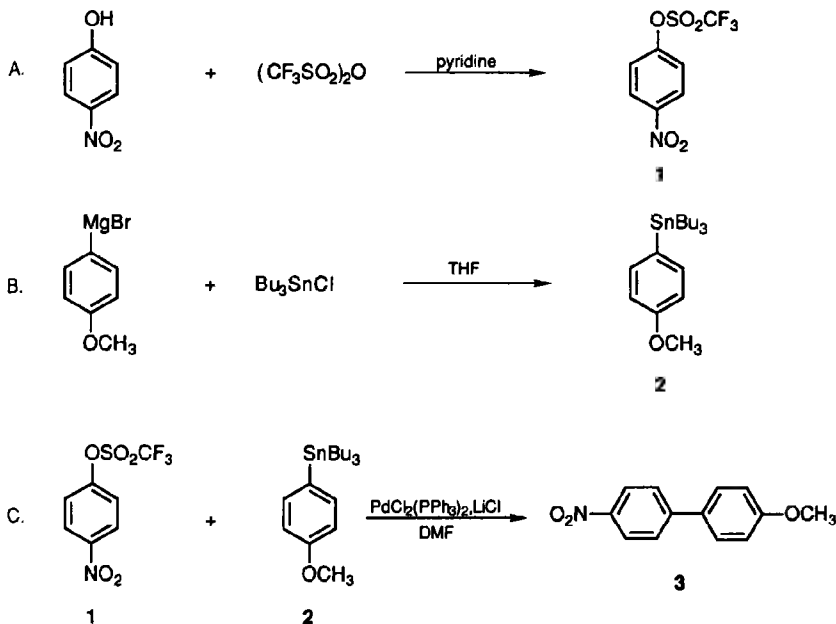
9-Borabicyclo[3.3.1]nonane (9-BBN) (8,9); (280-64-8)

Tetrakis(triphenylphosphine)palladium(0): Palladium, tetrakis(triphenylphosphine)-

(8); Palladium, tetrakis(triphenylphosphine)-, (T-4)- (9); (14221-01-3)

Triphenylphosphine: Phosphine, triphenyl- (8,9); (603-35-0)

4-METHOXY-4'-NITROBIPHENYL
(1,1'-Biphenyl, 4-methoxy-4'-nitro-)



Submitted by J. K. Stille, Antonio M. Echavarren, Robert M. Williams, and
 James A. Hendrix.¹

Checked and modified by Bryon A. Merrill and Larry E. Overman.

1. Procedure

Caution! Many organotin compounds are toxic.² Their preparation and use should be carried out in a well-ventilated hood.

A. 4-Nitrophenyl trifluoromethanesulfonate (1). A dry, 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, nitrogen gas inlet, and rubber septum (Note 1) is charged sequentially with 10.0 g (71.9 mmol) of 4-nitrophenol and 38 mL of pyridine (Note 2). The stirred solution is cooled to 0°C and 13.5 mL (80 mmol) of trifluoromethanesulfonic anhydride (Note 3) is added through the septum via a syringe. The rate of addition is such that the internal temperature of the flask never exceeds 25°C (Note 4). The solution is allowed to warm slowly to room temperature and is maintained at room temperature for 25 hr. The reaction is quenched by pouring it into a 250-mL separatory funnel that contains 100 mL of water and 50 mL of diethyl ether. The two phases are separated and the aqueous phase is extracted with four additional 50-mL portions of diethyl ether. The combined organic fractions are dried over magnesium sulfate, filtered, and concentrated to provide 18.7 g of crude **1** as a yellow, crystalline, solid.

The crude product is dissolved in 50 mL of diethyl ether and adsorbed onto 20 g of Celite 521 by evaporation of the diethyl ether under reduced pressure. The dry Celite 521 is then added to the top of a column containing 200 g of silica gel (32-63 micron) and the column is eluted with a mobile phase of 9:1 hexanes-ethyl acetate. The fractions containing the product ($R_f = 0.50$, 9:1 hexanes-ethyl acetate) are collected and concentrated under reduced pressure to yield 17.7 g (91%) of **1** as a colorless, crystalline, solid (Note 5).

B. Tributyl(4-methoxyphenyl)stannane (2). A dry, 250-mL, three-necked, round-bottomed flask, equipped with a reflux condenser, magnetic stirring bar, and nitrogen gas inlet, is charged with 2.91 g (120 mmol) of magnesium turnings (Notes 1

and 6). The flask is fitted with a rubber septum and charged sequentially via syringe with 85 mL of tetrahydrofuran (Note 7), 14.0 mL (112 mmol) of 4-bromoanisole (Note 8), and 0.05 mL of methyl iodide (Note 9). The rubber septum is immediately replaced with a Teflon stopper. Within 5 min, the reaction spontaneously warms to reflux temperature and continues to boil for approximately 10 min. The reaction is stirred an additional 2 hr without external heating or cooling. The flask is fitted with a rubber septum and 30.5 mL (112 mmol) of tributyltin chloride is added to the green solution via a syringe (Note 10). The septum is again replaced with a Teflon stopper and the reaction is heated at reflux for 12 hr.

Upon cooling to room temperature, a gray precipitate forms and the reaction is quenched with 220 mL of saturated, aqueous ammonium chloride. The resulting mixture is poured into a 1-L separatory funnel and extracted with 220 mL of diethyl ether. The organic fraction is washed two times with 100 mL of water, and once with 100 mL of brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide 44.1 g of crude product as a pale yellow oil. Purification of this material by bulb-to-bulb distillation (140-145°C, 0.5 mm) (Note 11) into a chilled (-78°C) receiving flask yields 41.0 g (92%) of **2** as a clear, colorless oil (Note 12).

C. 4-Methoxy-4'-nitrobiphenyl (3). A dry, 500-mL, three-necked, round-bottomed flask equipped with a reflux condenser, magnetic stirring bar, nitrogen gas inlet, and rubber septum (Note 1) is charged sequentially with 300 mL of anhydrous N,N-dimethylformamide (Note 13), 15.0 g (55.4 mmol) of 4-nitrophenyl trifluoromethanesulfonate (**1**), 27.8 g (70.0 mmol) of tributyl(4-methoxyphenyl)stannane (**2**) (Note 14), 7.5 g of dry lithium chloride (Note 15), and 1.6 g (4 mol percent) of bis(triphenylphosphine)palladium(II) chloride (Note 16). The rubber septum is replaced with a Teflon stopper and the yellow mixture is heated at 100-105°C for 2.5 hr. After approximately 20 min, the reaction turns dark brown.

The reaction mixture is cooled to room temperature and then vacuum-filtered through a 350-mL, medium frit, sintered-glass Büchner funnel that is filled to a height of 4 cm with ethyl acetate-impregnated Celite 521. Four 100-mL portions of ethyl acetate are used to wash the pad of Celite 521. The filtrate is partially concentrated by removal of ethyl acetate under reduced pressure. The resulting brown liquid is slowly poured into 1.5 L of water. After standing for 8 hr, the precipitate is collected by vacuum filtration and air dried. The solid is dissolved in 500 mL of acetonitrile, the resulting solution is poured into a 1-L separatory funnel, and is washed with three 300-mL portions of hexanes. The acetonitrile layer is concentrated to provide 24 g of crude product as a brown solid.

The crude product is dissolved in a minimum amount of dichloromethane and adsorbed onto 25 g of silica gel (32-63 micron) by subsequent evaporation of the dichloromethane under reduced pressure. The sample of dry, dark brown silica gel is added to the top of a column containing 500 g of silica gel (32-63 micron) with a mobile phase of hexanes. The polarity of the mobile phase is gradually increased from hexanes to 95:5 hexanes-ethyl acetate. The fractions containing the desired product ($R_f = 0.26$, 95:5 hexanes-ethyl acetate) are combined and concentrated under reduced pressure to yield 6.9 g of **3** as a yellow solid. Additional purification is required to remove traces of tin by-products. Compound **3** is dissolved in 70 mL of ethyl acetate and stirred over 70 mL of saturated, aqueous potassium fluoride for 24 hr. The two phases are separated and the organic phase is dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting yellow solid is recrystallized from ethyl alcohol to provide 6.1 g (48%, 2 crops) of **3** as yellow needles (Notes 17, 18, and 19).

2. Notes

1. All glassware is oven-dried at 140°C overnight and assembled while hot under a nitrogen atmosphere.

2. 4-Nitrophenol (99%+) is purchased from the Aldrich Chemical Company, Inc., as a golden yellow solid and used as received. Pyridine is freshly distilled from calcium hydride.

3. Trifluoromethanesulfonic anhydride is purchased from the Aldrich Chemical Company, Inc., and used as received. It may also be prepared from trifluoromethanesulfonic acid.³

4. The reaction turns deep red upon addition of the anhydride.

5. 4-Nitrophenyl trifluoromethanesulfonate exhibits the following properties: mp 54-55°C (lit.⁴ 53°C); IR (KBr) cm^{-1} : 3125, 3094, 1625, 1590, 1537, 1487, 1423, 1352, 1253, 1214, 1137, 1012, 900, 862, 759, 744, 692, 613; ^1H NMR (300 MHz, CDCl_3) δ : 7.50 (d, 2 H, $J = 9.2$), 8.37 (d, 2 H, $J = 9.2$); high resolution mass spectrum (isobutane CI): 271.9848 (271.9840 calcd for $\text{C}_7\text{H}_5\text{F}_3\text{NO}_5\text{S}$).

6. Magnesium turnings (99.99%) are purchased from Johnson Matthey/Alfa Products and used as received.

7. Tetrahydrofuran is freshly distilled from sodium benzophenone ketyl.

8. 4-Bromoanisole is purchased from the Aldrich Chemical Company, Inc., and used as received.

9. Methyl iodide is purchased from the Aldrich Chemical Company, Inc., and used as received. Methyl iodide is used as a catalyst to initiate the Grignard reaction.

10. Tributyltin chloride is purchased from the Aldrich Chemical Company, Inc., and used as received. The reaction warms upon the introduction of tributyltin chloride, but it does not boil spontaneously.

11. Tributyl(4-methoxyphenyl)stannane is reported to boil at 158-160°C (0.5 mm).⁵

12. Tributyl(4-methoxyphenyl)stannane exhibits the following properties: ¹H NMR (500 MHz, CDCl₃) δ: 0.88 (t, 9 H, J = 7.3), 1.02 (m, 6 H), 1.33 (m, 6 H), 1.53 (m, 6 H), 3.80 (s, 3 H), 6.90 (d, 2 H, J = 8.5), 7.37 (d, 2 H, J = 8.5). The peaks at 1.02 and 7.37 ppm show coupling with tin; mass spectrum (isobutane CI) 399, 397, 395, 291, 289, 287. The product is at least 97% pure by GC analysis (30 m, Supelco SPB-1 fused silica column).

13. Anhydrous N,N-dimethylformamide (water <0.005%) is purchased from the Aldrich Chemical Company, Inc., and transferred via cannula directly from the Sure/Seal bottle into the reaction flask. The solvent is deoxygenated by bubbling nitrogen through it for 45 min prior to the addition of compound 2.

14. Tributyl(4-methoxyphenyl)stannane (2) is added to the reaction flask via a 30-mL syringe.

15. Lithium chloride is dried by heating at 130°C under reduced pressure (0.5 mm) for 24 hr.

16. Bis(triphenylphosphine)palladium(II) chloride (98%) is purchased from the Aldrich Chemical Company, Inc., and used as received.

17. 4-Methoxy-4'-nitrobiphenyl (3) has the following properties: mp 109-110°C (lit.⁶ 111°C); IR (KBr) cm⁻¹: 3062, 2968, 2838, 1600, 1509, 1487, 1345, 1253, 1034, 1017, 857, 845, 830, 817, 757, 724, 696; ¹H NMR (500 MHz, CDCl₃) δ: 3.88 (s, 3 H), 7.01 (d, 2 H, J = 8.7), 7.58 (d, 2 H, J = 8.7), 7.68 (d, 2 H, J = 8.7), 8.26 (d, 2 H, J = 8.7); ¹³C NMR (125 MHz, CDCl₃) δ: 55.4, 114.5, 124.1, 127.0, 128.5, 131.0, 146.4, 147.1, 160.4; mass spectrum (isobutane CI): 230 (MH). Anal. Calcd for C₁₃H₁₁NO₃: C, 68.10; H, 4.84; N, 6.11. Found: C, 67.99; H, 4.87; N, 6.13.

18. The checkers also recover 170 mg (2%) of 4,4'-dimethoxybiphenyl (4) (R_f = 0.38, 95:5 hexanes-ethyl acetate) and 310 mg (3%) of 4-amino-4'-methoxybiphenyl

(5) ($R_f = 0.28$, 4:1 hexanes-ethyl acetate) as minor byproducts. Compound 5 is recovered from the column by increasing the eluent polarity to 4:1 hexanes-ethyl acetate.

4,4'-Dimethoxybiphenyl (4) has the following properties: mp 175-177°C (lit.⁷ 176-178°C); IR (KBr) cm^{-1} : 2958, 2914, 2840, 1608, 1503, 1277, 1251, 1184, 1042, 1012, 825, 810; ^1H NMR (500 MHz, CDCl_3) δ : 3.85 (s, 6 H), 6.96 (d, 4 H, $J = 8.7$), 7.48 (d, 4 H, $J = 8.7$); ^{13}C NMR (125 MHz, CDCl_3) δ : 55.3, 114.1, 127.7, 133.5, 158.7; high resolution mass spectrum (70 eV, EI): 214.0993 (214.0994 calcd for $\text{C}_{14}\text{H}_{14}\text{O}_2$).

4-Amino-4'-methoxybiphenyl (5) has the following properties: mp 143-144°C (lit.⁸ 144-145.5°C); IR (KBr) cm^{-1} : 3396, 3334, 3224, 3033, 2965, 2837, 1636, 1608, 1500, 1270, 1241, 1181, 1035, 1015, 817; ^1H NMR (500 MHz, CDCl_3) δ : 3.69 (broad s, 2 H), 3.84 (s, 3 H), 6.75 (d, 2 H, $J = 8.5$), 6.95 (d, 2 H, $J = 8.8$), 7.37 (d, 2 H, $J = 8.4$), 7.46 (d, 2 H, $J = 8.8$); ^{13}C NMR (125 MHz, CDCl_3) δ : 55.3, 114.1, 115.4, 127.4, 127.6, 131.3, 133.8, 145.2, 158.4; high resolution mass spectrum (70 eV, EI): 199.0990 (199.0997 calcd for $\text{C}_{13}\text{H}_{13}\text{NO}$).

19. The checkers found that using tetrakis(triphenylphosphine)palladium(0) as the catalyst and dioxane as the solvent resulted in significant reduction of the nitro-substituent in the coupled product.⁹ Biphenyls 3 and 5 are obtained in ratios as high as one to one under these conditions.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

The introduction of a bond between two aromatic rings is a familiar problem in organic synthesis. A wide variety of classical and non-classical methods are available for the preparation of unsymmetrical biaryl compounds.¹⁰ However, many of these methods are non-selective and require harsh conditions in order to obtain reasonable yields. A relatively mild and versatile method for the formation of carbon-carbon bonds is the palladium-catalyzed coupling of functionalized organostannanes with organic electrophiles.^{11,12} Aryl halides¹³ and aryl trifluoromethanesulfonates (triflates)^{9,14} couple with organostannanes to provide a selective method for the formation of aryl-aryl bonds. Aryl triflates are especially important starting materials because of their stability and ease of formation.^{15,16}

The palladium-catalyzed cross-coupling reaction featured in this procedure occurs under neutral conditions in the presence of many synthetically useful functional groups (e.g. alcohol, ester, nitro, acetal, ketone, and aldehyde). The reaction works best in *N,N*-dimethylformamide with bis(triphenylphosphine)palladium(II) chloride, $\text{PdCl}_2(\text{PPh}_3)_2$, as the catalyst. Lithium chloride is added to prevent decomposition of the catalyst.^{14a,b} It is presumed that conversion of the intermediate aryl palladium triflate to an aryl palladium chloride is required for the transmetalation step to proceed.⁹

In a recent study examining ligand effects on the palladium-catalyzed cross-coupling reaction between aryl triflates and vinylstannanes, tri-2-furylphosphine and triphenylarsine were observed to provide significant rate enhancements (10^2 - 10^3 greater than with triphenylphosphine-based catalysts).¹⁷ Although not reported, these ligands may also be useful for aryl-aryl cross-coupling reactions.

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16. Aryl fluorosulfonates have recently been reported as less expensive alternatives to aryl triflates. Compound **3** has been synthesized in 50% isolated yield using 4-nitrophenyl fluorosulfonate as the electrophilic partner in the cross-coupling reaction. Roth, G. P.; Fuller, C. E. *J. Org. Chem.* **1991**, *56*, 3493-3496.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

4-Methoxy-4'-nitrobiphenyl: 1,1'-Biphenyl, 4-methoxy-4'-nitro- (9); (2143-90-0)

4-Nitrophenyl trifluoromethanesulfonate: Methanesulfonic acid, trifluoro-, p-nitrophenyl ester (8); Methanesulfonic acid, trifluoro-, 4-nitrophenyl ester (9); (17763-80-3)

4-Nitrophenol: Phenol, p-nitro- (8); Phenol, 4-nitro- (9); (100-02-7)

Trifluoromethanesulfonic anhydride: Methanesulfonic acid, trifluoro-, anhydride (8,9); (358-23-6)

Tributyl(4-methoxyphenyl)stannane: Stannane, tributyl(4-methoxyphenyl)- (10); (70744-47-7)

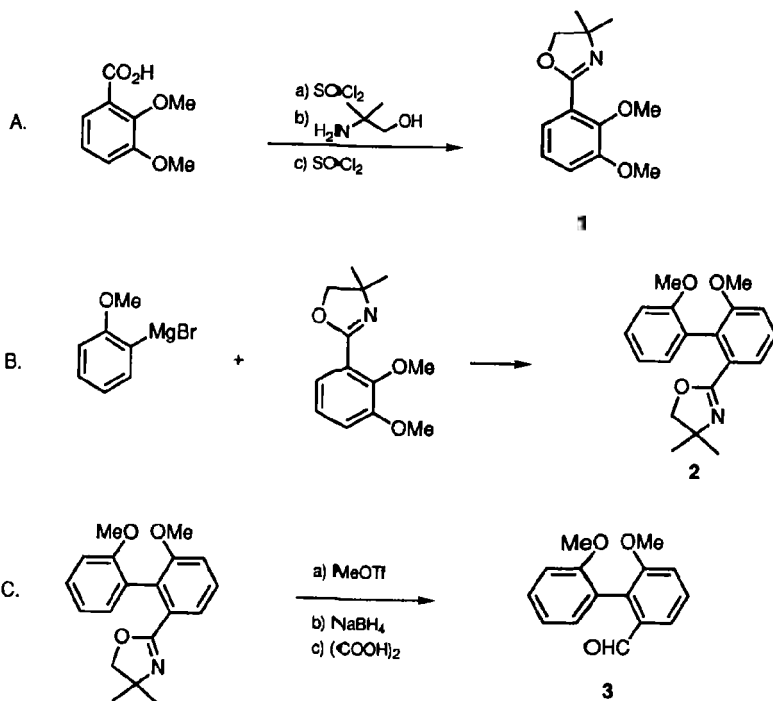
4-Bromoanisole: Anisole, p-bromo- (8); Benzene, 1-bromo-4-methoxy- (9); (104-92-7)

Methyl iodide: Methane, iodo- (8,9); (74-88-4)

Tributyltin chloride: Stannane, tributylchloro- (8,9); (1461-22-9)

Bis(triphenylphosphine)palladium(II) chloride: Palladium, dichlorobis(triphenylphosphine)- (8,9); (13965-03-2)

2,2'-DIMETHOXY-6-FORMYLBIPHENYL
((1,1'-Biphenyl)-2-carboxaldehyde, 2,6-dimethoxy-)



Submitted by Albert I. Meyers and Mark E. Flanagan.¹

Checked by Chris H. Senanayake and Ichiro Shinkai.

1. Procedure

Caution! This procedure should be performed in a well-ventilated hood.

A. *2-(2,3-Dimethoxyphenyl)-4,4-dimethyl-2-oxazoline*. To a 100-mL, round-bottomed flask, fitted with a magnetic stirring bar and a reflux condenser and placed in an ice-water bath, is added 24.5 g (0.206 mol) of thionyl chloride (Note 1). To this is added 12.2 g (0.067 mol) of 2,3-dimethoxybenzoic acid (Note 2). The resulting mixture is stirred at 0°C for 1 hr and then at room temperature for 24 hr. Excess thionyl chloride is removed by rotary evaporation (HOOD!) and the residue is distilled using a Kugelrohr apparatus at 105°C (0.05 mm) to give 12.7-13.1 g of 2,3-dimethoxybenzoyl chloride, which crystallizes on cooling (Note 3).

The acid chloride, 12.7 g, is dissolved in 60 mL of dichloromethane and transferred to a 300-mL round-bottomed flask fitted with a magnetic stirring bar and a 100-mL, pressure-equalizing dropping funnel. The solution is cooled to 0°C in an ice bath. 2-Amino-2-methyl-1-propanol (12.5 g, 0.140 mol) dissolved in 50 mL of dichloromethane is added dropwise to the cold solution over 15 min. The reaction mixture is allowed to warm to room temperature and stirring is continued for 2 hr. The white precipitate (Note 4) is removed by filtration and the mother liquor is removed by rotary evaporation to afford 15.7 g of the amido alcohol (Note 5). The amido alcohol is redissolved in 100 mL of dichloromethane and added to a 300-mL round-bottomed flask fitted with a reflux condenser and a magnetic stirring bar. Thionyl chloride (24.5 g, 0.206 mol) is added dropwise and the resulting mixture is stirred at room temperature for 1.5 hr (Note 6). The reaction mixture is cooled to 0°C (ice-water bath) and to it is added slowly 50 mL of cold water followed by approximately 50 mL of aqueous 40% sodium hydroxide solution, which neutralizes the reaction mixture to approximately pH 11. Saturated sodium chloride solution (approximately 50 mL) is added and the contents of the flask are transferred to a 1-L separatory funnel. The

lower phase (CH_2Cl_2 solution) is removed and set aside while the upper, aqueous phase is extracted once with 50 mL of dichloromethane. The dichloromethane extracts are combined and dried over magnesium sulfate. The solution is then filtered through Celite and concentrated under reduced pressure to leave crude 2-(2,3-dimethoxyphenyl)-4,4-dimethyl-2-oxazoline (1). The latter is distilled in a Kugelrohr apparatus at 110°C (0.05 mm) to give 12.7-13.3 g (81-85%) (Note 7).

B. 2,2'-Dimethoxy-6-(4",4"-dimethyloxazoliny)biphenyl. Magnesium turnings (3.3 g, 0.14 g-atom, Note 8) and 100 mL of dry ether (Note 9) are added to a flame-dried, 1-L, round-bottomed flask under a nitrogen atmosphere. The flask is fitted with a 250-mL addition funnel, reflux condenser, and magnetic stirring bar, and placed under a slow nitrogen flow. A few crystals of iodine are added to the reaction vessel followed by dropwise addition of 18 g (0.12 mol) of 2-bromoanisole (Note 10) in 150 mL of anhydrous ether (Note 11). When the addition is complete, the reaction mixture is stirred for 2 hr at room temperature. When it is apparent that formation of the Grignard solution has consumed most of the magnesium turnings, a solution of the dimethoxyphenyloxazoline, 11.2 g (0.048 mol) in 300 mL of anhydrous tetrahydrofuran (Note 12), is added dropwise at room temperature to the stirred Grignard solution. After addition is complete, stirring of the dark solution is continued for 24 hr or until reaction is complete (Note 13). The reaction mixture is quenched by careful addition of saturated ammonium chloride (50 mL) followed by addition of 50 mL of water. The contents are transferred to a 1-L separatory funnel and the lower aqueous phase is separated while the upper organic phase is set aside. The aqueous phase is returned to the separatory funnel and extracted once with 50 mL of ether; both ethereal phases are then combined, dried over magnesium sulfate, and filtered and concentrated under reduced pressure. There is obtained 19.2 g of a yellow solid that contains, in addition to the biphenyl, some anisole and other contaminants (e.g., starting materials). The volatile impurities are removed by Kugelrohr or other short path

distillation (105°C, 0.05 mm, 15 min) to leave 14.2 g (96%) of crude biphenyl product. Purification is performed by recrystallization from ethyl acetate-hexane (1:1) to give 12.2-13.0 g (80-85%) of pure material (Notes 14, 15).

C. 2,2'-Dimethoxy-6-formylbiphenyl. To a flame-dried, 1-L, round-bottomed flask, under nitrogen, and fitted with a magnetic stirring bar is added 12.2 g (0.039 mol) of pure biphenyloxazoline **2** in 300 mL of dry dichloromethane (Note 16). To this is added 7.9 g (0.048 mol) of methyl trifluoromethanesulfonate (Note 17) and the chilled solution is stirred at room temperature for 2-3 hr (Note 18). The solution of quaternized oxazoline is cooled to 0°C in an ice-water bath. Separately, 3.3 g (0.87 mol) of sodium borohydride is slurried at 0°C with 125 mL of absolute ethanol. The chilled slurry is added slowly, to control foaming, to the reaction mixture. When the addition is complete, the mixture is stirred at 0°C for 45 min and the contents of the flask are evaporated under reduced pressure. The resulting solid residue is dissolved in 400 mL of 4:1 tetrahydrofuran-water and 19.5 g (0.217 mol) of oxalic acid is added in portions (exotherm). The mixture is stirred at room temperature for 16-18 hr (Note 19). Tetrahydrofuran is removed under rotary evaporation to leave behind an aqueous slurry that is washed in a separatory funnel with pentane-ether (1:1, 2 x 100 mL). The upper layer is removed and the aqueous layer is extracted again with 50 mL of pentane-ether. The organic layers are combined and washed with 50 mL of aqueous 10% sodium bicarbonate and then with 50 mL of saturated brine. The aqueous washes are also back-extracted with pentane-ether which is combined with the other organic solutions. The organic layers are dried over sodium sulfate (anhydrous) and the solution is filtered through Celite. Concentration of the solution under reduced pressure gives 7.5 g (75-83%) of the final biphenyl aldehyde, mp 65-67°C. Recrystallization from 2-propanol gives 6.5 g of pure material (Notes 20, 21).

2. Notes

1. Thionyl chloride was purchased from Fisher Scientific Company.
2. 2,3-Dimethoxybenzoic acid was used as received from Aldrich Chemical Company, Inc.
3. The melting point was 53-54°C.
4. This is the hydrochloride of 2-amino-2-methyl-1-propanol.
5. The melting point was 77-80°C after air drying for several hours.
6. The formation of the 2,3-dimethoxyphenyloxazoline (1) can be readily followed by removing aliquots, neutralizing with aqueous sodium hydroxide, and checking on TLC using silica gel and eluting with hexane-acetone, 85:15; R_f is 0.29.
7. The physical properties are as follows: mp 44-46°C, $^1\text{H-NMR}$ (250 MHz, CDCl_3) δ : 1.36 (s, 6 H), 3.83 (s, 6 H), 4.08 (s, 2 H), 6.96 (dd, 1 H, $J = 8.2, 1.9$), 7.02 (dd, 1 H, $J = 8.2, 7.5$), 7.29 (dd, 1 H, $J = 7.5, 1.9$).
8. Magnesium turnings were purchased from J. T. Baker Chemical Company.
9. Ether was distilled from benzophenone ketyl under nitrogen. The checkers used ether dried over 4 Å molecular sieves, under nitrogen, for 2 days and obtained the same results.
10. 2-Bromoanisole was purchased, and used without further purification, from Aldrich Chemical Company, Inc.
11. Warming of the reaction vessel with a water bath ($\sim 30^\circ\text{C}$) tends to expedite the initiation of the Grignard reagent.
12. Anhydrous tetrahydrofuran (THF) was distilled from benzophenone ketyl under nitrogen. The checkers used THF dried over 4 Å molecular sieves, under nitrogen, for 2 days and obtained the same results.

13. The reaction is followed by TLC (silica, hexane-acetone, 85:15) and shows the disappearance of the dimethoxyphenyloxazoline 1 at R_f 0.29 and the appearance of the biphenyl 2 at R_f 0.18.

14. The physical properties are as follows: mp 127-129°C; ^1H NMR (250 MHz, CDCl_3) δ : 1.18 (s, 3 H), 1.19 (s, 3 H), 3.59 (d, 1 H, $J = 8.1$), 3.72 (d, 1 H, $J = 8.1$), 3.75 (s, 6 H), 6.98 (om, 2 H), 7.05 (dd, 1 H, $J = 7.1, 2.4$), 7.15 (dd, 1 H, $J = 7.4, 1.7$), 7.29 (dd, 1 H, $J = 7.6, 1.8$), 7.34-7.39 (om, 2 H).

15. If crude material is used in Step C, the yield of final product is approximately 50-58%.

16. Dichloromethane was dried by distilling from calcium hydride. The checkers used dichloromethane (reagent grade) kept over 4 Å molecular sieves for 2 days to obtain the same results.

17. Methyl trifluoromethanesulfonate was purchased from Aldrich Chemical Company, Inc.

18. Stirring is continued until quaternization of the oxazoline 2 is complete. This is easily monitored by TLC which shows only baseline salt (silica, hexane-acetone) and complete absence of the biphenyloxazoline at R_f 0.18.

19. The checkers report that the reaction can be followed by TLC, indicating disappearance of starting material and appearance of the aldehyde ($R_f = 0.75$, hexane-ethyl acetate, 75:25).

20. The physical properties are as follows: mp 75-76°C; ^1H NMR (250 MHz, CDCl_3) δ : 3.74 (s, 3 H), 3.78 (s, 3 H), 7.01 (d, 1 H, $J = 8.3$), 7.06 (m, 1 H), 7.22 (dd, 1 H, $J = 7.9, 1.7$), 7.23 (dd, 1 H, $J = 7.4, 1.8$), 7.39-7.49 (om, 2 H), 7.63 (dd, 1 H, $J = 7.8, 1.0$), 9.68 (d, 1 H, $J = 0.8$).

21. The submitters report that this procedure can also produce the corresponding biphenyl carboxylic acid by omitting the quaternization-reduction step and subjecting the biphenyloxazoline 2 to hydrolysis as follows:

A slurry of 2 (0.1 M) in 4 M hydrochloric acid is heated at reflux for 16 hr. The solution is concentrated to dryness by rotary evaporation and the crude carboxylic acid, derived from 2, is recrystallized from hexane-ethyl acetate-isopropyl alcohol (2:1:1) furnishing pure material in 80% yield, mp 196-197°C.

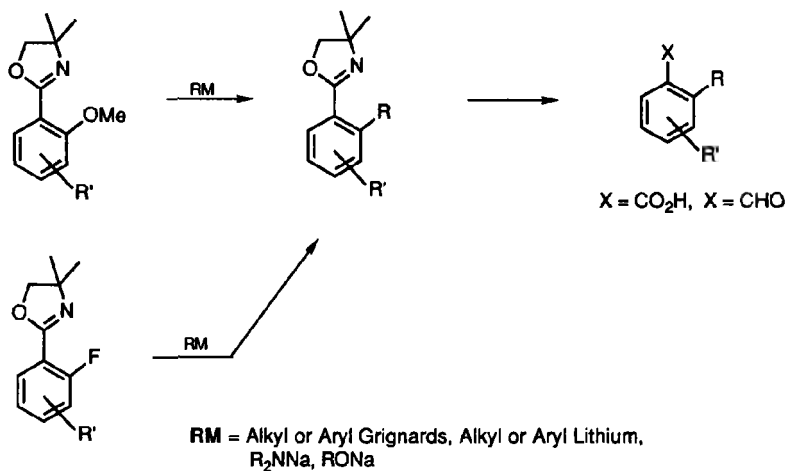
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

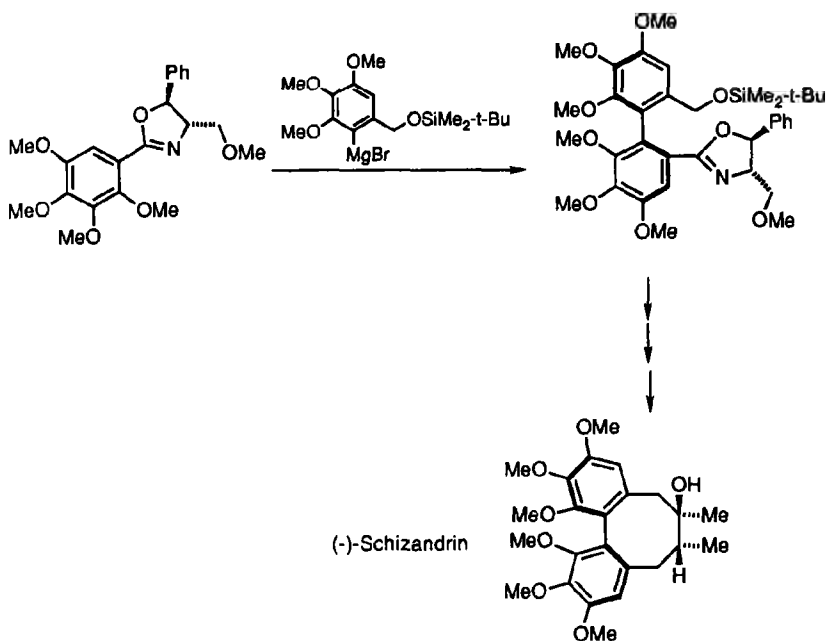
The use of oxazolines in aromatic substitution is a valuable synthetic tool.² The o-methoxy- or o-fluorophenyloxazoline reacts readily with a variety of organolithium or Grignard reagents to displace only the ortho substituent. In this fashion a number of ortho-substituted benzoic acids, benzaldehydes, and unsymmetrical biphenyls are accessible. The reaction takes place under very mild conditions, usually at or below room temperature, and thus allows a number of other sensitive groups to be present.

Scheme 1



In addition to the simple substitutions shown in Scheme 1, this reaction has been used in a variety of complex systems as a route to optically active substances. For example, use of chiral oxazolines in this coupling process has led to an asymmetric synthesis of (-)-steganone,³ podophyllotoxin,⁴ (-)-schizandrin,⁵ and (+)-phylictralin.⁶ The synthesis of (-)-schizandrin is sketched in Scheme 2.

Scheme 2



This method described here for preparing unsymmetrical biphenyls compares favorably with other recent and classical routes.⁷⁻¹⁰

1. Department of Chemistry, Colorado State University, Fort Collins, CO 80523.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

- 2,2'-Dimethoxy-6-formylbiphenyl: [1,1'-Biphenyl]-2-carboxaldehyde, 2',6-dimethoxy- (11); (87306-84-1)
- 2-(2,3-Dimethoxyphenyl)-4,4-dimethyl-2-oxazoline: Oxazoline, 2-(2,3-dimethoxyphenyl)-4,5-dihydro-4,4-dimethyl- (9); (57598-32-0)
- Thionyl chloride (8,9); (7719-09-7)
- 2,3-Dimethoxybenzoic acid: Benzoic acid, 2,3-dimethoxy- (9); (1521-38-6)

2,3-Dimethoxybenzoyl chloride: Benzoyl chloride, 2,3-dimethoxy- (9); (7169-06-4)

2-Amino-2-methyl-1-propanol: 1-Propanol, 2-amino-2-methyl- (8,9); (124-68-5)

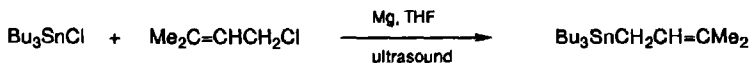
2,2'-Dimethoxy-6-(4",4"-dimethyloxazoliny)biphenyl: Oxazole, 2-(2',6-dimethoxy[1,1'-biphenyl]-2-yl)-4,5-dihydro-4,4-dimethyl- (9); (57598-39-7)

2-Bromoanisole: Anisole, o-bromo- (8); Benzene, 1-bromo-2-methoxy- (9); (578-57-4)

Methyl trifluoromethanesulfonate: Methanesulfonic acid, trifluoro-, methyl ester (8,9); (333-27-7)

Oxalic acid (8); Ethanedioic acid (9); (144-62-7)

TRIBUTYL(3-METHYL-2-BUTENYL)TIN
(Stannane, tributyl(3-methyl-2-butenyl)-)



Submitted by Yoshinori Naruta, Yutaka Nishigaichi, and Kazuhiro Maruyama.¹

Checked by Bruce M. Branen and Leo A. Paquette.

1. Procedure

Caution! This experiment should be performed with gloves in an efficient hood in order to avoid the contact of toxic tributyltin derivatives with the skin and to avoid their unpleasant odor. One should wear earmuffs during operation of an ultrasound processor.

A dry, 500-mL, three-necked flask appropriately shaped to accommodate the horn of an ultrasonic processor is equipped with a thermometer and a pressure-equalizing dropping funnel to which a nitrogen inlet is attached. A nitrogen atmosphere is established in the flask, which is charged with 100 mL of anhydrous tetrahydrofuran (THF) (Note 1), 3.04 g (0.125 mol) of magnesium (Mg) turnings (Note 2), 32.5 g (0.100 mol) of tributyltin chloride (Note 2), and a small piece of iodine (optional), and then immersed in an ice-salt bath. After the temperature of the solution falls below 15°C, 13.4 mL (0.120 mol) of 1-chloro-3-methyl-2-butene (Note 3) in 50 mL of THF is added dropwise over 30-60 min while maintaining the temperature at less than 20°C (Note 4) under sonication at an output power of 30-75W (Note 5). After the addition is complete, sonication is continued for a further 30-45 min (Note 6) to complete the reaction. The reaction mixture is poured into 400 g of ice water and the

mixture is extracted with three 100-mL portions of ether. The combined ethereal solutions are washed with 50 mL of water and 50 mL of brine, dried over anhydrous magnesium sulfate, and evaporated under aspirator pressure to yield a colorless oil. This oil is further evacuated (1 mm) at room temperature for 1 hr (Note 7) to give 36 g (100%) of tributyl(3-methyl-2-butenyl)tin. This material is sufficiently pure for direct use in most reactions, but can be purified by distillation to afford 33.2 g (92%) of colorless oil, bp 105-107°C (0.01 mm) (Notes 8-10).

2. Notes

1. THF is distilled from benzophenone ketyl and stored over sodium wire under a nitrogen atmosphere. For the drying procedure and caution, see *Org. Synth., Coll. Vol. VII* 1990, 451 and *Org. Synth., Coll. Vol. V* 1973, 976 respectively.

2. Magnesium turnings were purchased from Wako Pure Chemical Industries and the Aldrich Chemical Company, Inc. Tributyltin chloride was obtained from Tokyo Kasei Kogyo and the Aldrich Chemical Company, Inc. They were used without further purification.

3. As purchased from the Aldrich Chemical Company, Inc., this chloride contains 5-10% of 1-chloro-1-methyl-3-butene. Contamination by this isomeric chloride does not affect the yield of tributyl(3-methyl-2-butenyl)tin.

4. The reaction temperature should be kept below 20°C to prevent side reactions. If the temperature exceeds 20°C, one should stop both the addition of the prenyl chloride and the ultrasound irradiation, and wait for the reaction temperature to fall below 15°C.

5. The submitters used Heat Systems-Ultrasonics Model W-220 (maximum output power 200W) with a standard horn. The checkers used a Sonics and Materials Inc. Vibra-Cell High Intensity Ultrasonic Processor (maximum power outlet 600W)

fitted with a 13-in extender probe. If the applied ultrasonic processor does not have a power meter, one can judge the applied power by the occurrence of vigorous stirring of the Mg turnings around the immersed ultrasonic horn. If the Mg turnings settle to the bottom of the flask, the applied sonication power is insufficient.

For reaction on a 10-mmol scale, an ultrasonic cleaner with sufficient output power (e.g., Branson Model B-220) can be used for external irradiation.

6. After completion of the reaction, ultrasonic irradiation for an unnecessarily long period causes decomposition of the allyltributyltin. The end of the reaction can be determined by a faint turbidity in the solution and by darkening of the brilliant Mg surface.

7. Through this treatment, most of the low-boiling impurity can be removed.

8. Good purity (95-98%) is observed by GLC (glass capillary column, OV-101, 0.33 mm x 25) at an oven temperature of 200°C.

9. Because of modest thermal instability of the material, one should distill at a bath temperature below 150°C. When the bath temperature exceeds 150°C, considerable decomposition of the allylic tributyltin occurs and a poorer yield is realized. The checkers measured a bp of 100°C at 0.1 mm.

10. The spectrum is as follows: ^1H NMR (400 MHz, CDCl_3) δ : 0.83 (m, 6 H, SnCH_2), 0.89 (t, 9 H, $J = 7$, CH_3 of Bu), 1.29 (m, 6 H, SnCH_2CH_2), 1.47 (m, 6 H, CH_2CH_3), 1.57 (s, 3 H, cis- CH_3), 1.64 (d, 2 H, $J = 9$, $\text{CH}_2\text{CH}=\text{C}$), 1.67 (s, 3 H, trans- CH_3), 5.28 (broad t, 1 H, $J = 9$, $\text{CH}=\text{C}$); ^{13}C NMR (75 MHz, CDCl_3) δ : 9.4, 10.7, 13.7, 17.4, 25.5, 27.4, 29.3, 123.0, 125.3; ^{119}Sn NMR (120 MHz, CDCl_3) δ : -13.4.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

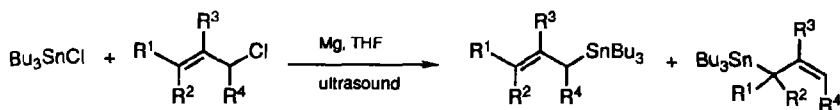
This procedure describes ultrasound-promoted Barbier-type cross coupling of an allylic chloride with tributyltin chloride.² Allylic trialkyltin derivatives have also been prepared by (i) a coupling reaction of a trialkyltin chloride with an allyl Grignard reagent³⁻⁵ or allyllithium,^{6,7} and allyl derivatives with stannyl metals,⁸⁻¹² (ii) stannylation of allylic sulfides,¹² sulfones,^{13,14} selenoxides,¹⁵ alcohols,¹⁶ and allyl palladium.¹⁷⁻¹⁹ The method with an allylic Grignard reagent prepared in advance of the coupling reaction is an alternative to this method, but the ultrasonic procedure is more convenient and effective. For the preparation of simple allyltributyltin or its homologues, the present method has advantages over other methods, especially because of easy manipulation and scale-up, reproducibility, and yield.

This procedure is representative of a general and versatile method for the preparation of allylic tributyltins. Other allylstannanes prepared using this method are shown in the Table.

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TABLE
COUPLING OF ALLYLIC HALIDES WITH TRIBUTYLSTANNYL CHLORIDE^a



R ¹	R ²	R ³	R ⁴	Total Yield, % (α- + γ-isomers)	Isomeric ratio, α : γ
H	H	H	H	100	-
H	H	Me	H	96	-
Me	H	H	H	100	1 : 1 ^b
Me	H	H	Me	52 ^c	-
Ph	H	H	H	100 ^d	1 : 0
CH ₂ =CH	H	H	H	96 ^e	1 : 0
MeCH=CH	H	H	H	100 ^f	1 : 0

^aAll reactions were performed on a 10-mmol scale.

^bThe α-adduct is a mixture of trans:cis = 55:45.

^cPure trans-2-chloro-3-pentene was used. The α-adduct is a mixture of trans:cis = 55:45.

^dNo cis isomer is formed.

^eThe stereoisomer ratio is trans:cis = 92:8.

^fThe trans,trans-isomer is obtained in >90% purity.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

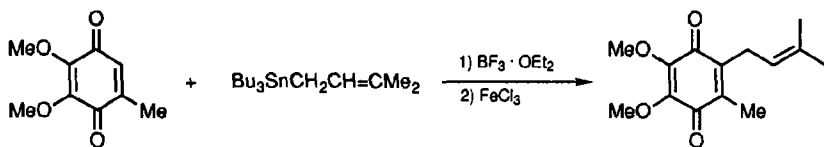
Tributyl(3-methyl-2-butenyl)tin: Stannane, tributyl(3-methyl-2-butenyl)- (9);
(53911-92-5)

Tributyltin chloride: Stannane, tributylchloro- (8,9); (1461-22-9)

1-Chloro-3-methyl-2-butene: 2-Butene, 1-chloro-3-methyl- (8,9); (503-60-6)

UBIQUINONE-1

(2,5-Cyclohexadiene-1,4-dione, 2,3-dimethoxy-5-methyl-6-(3-methyl-2-butenyl)-)



Submitted by Yoshinori Naruta and Kazuhiro Maruyama.¹

Checked by Steven W. Elmore and Leo A. Paquette.

1. Procedure

Caution! This experiment should be performed with gloves in an efficient hood in order to avoid the contact of toxic tributyltin derivatives with the skin and to avoid their unpleasant odor.

A 500-mL, three-necked, round-bottomed flask fitted with a low-temperature thermometer, 125-mL pressure-equalizing dropping funnel, and nitrogen gas inlet is flame-dried under vacuum, cooled to room temperature, and flushed with nitrogen. The flask is charged with 5.00 g (27.4 mmol) of 2,3-dimethoxy-5-methyl-1,4-benzoquinone (Note 1) as a solid followed by 100 mL of dry dichloromethane (Note 2) via syringe. The addition funnel is charged with 11.8 g (32.9 mmol) of tributyl(3-methyl-2-butenyl)tin (Note 3) in 100 mL of dry dichloromethane. The flask is immersed in an acetone/dry ice bath, the solution cooled to -78°C , and 10.1 mL (82.3 mmol) of boron trifluoride etherate (Note 4) is added dropwise from a syringe. Next, the stannane solution is added dropwise over a 30-min period. Following completion of

the addition, the cooling bath is removed and the reaction mixture is allowed to warm to room temperature. At -40°C, the color of the solution turns from deep red to yellow. When the reaction mixture reaches 0°C, it is treated with 100 mL of 10% hydrochloric acid, stirred for 5 min, and allowed to stand. The aqueous phase that separates is washed with dichloromethane (2 x 20 mL) and the combined organic layers are washed with water (2 x 20 mL) and brine (2 x 20 mL), dried over anhydrous magnesium sulfate, and concentrated. The residual yellow oil is dissolved in 200 mL of ether and this solution is added to 37.1 g (137 mmol) of ferric chloride hexahydrate $\text{FeCl}_3 \cdot 6 \text{H}_2\text{O}$ in 200 mL of water in a 500-mL conical flask. The resulting mixture is stirred for 8 hr at room temperature. The layers are then separated, the aqueous phase is extracted with ether (2 x 50 mL), and the combined organic solutions are stirred with 100 mL of 10% aqueous potassium fluoride for 2 hr (Note 5). The insoluble tin salts are separated by filtration (Note 6). The organic phase in the filtrate is washed with water (3 x 20 mL) and brine (3 x 20 mL), dried over anhydrous magnesium sulfate, and concentrated to give a deep red oil, that is purified by column chromatography (Note 7). The red-orange band is collected (1600-3000 mL) to give 6.15 g (90%) of 2,3-dimethoxy-5-methyl-6-(3-methyl-2-butenyl)-1,4-benzoquinone as a deep red oil (Note 8).

2. Notes

1. Commercial 2,3-dimethoxy-5-methyl-1,4-benzoquinone (Aldrich Chemical Company, Inc.) was used without further purification.
2. Dichloromethane was distilled from phosphorus pentoxide.
3. Tributyl(3-methyl-2-butenyl)tin was prepared according to the preceding procedure from 1-chloro-3-methyl-2-butene, tributyltin chloride, and magnesium.

4. Boron trifluoride etherate was purchased from Nacalai Tesque or Aldrich Chemical Company, Inc. and used without further purification. Since the purity of the BF_3 complex affects the yield of the quinone, reagent stored for a long period should be distilled prior to its use.

5. This facile method for removing organotin impurities was developed by Keck.²

6. Tin wastes are collected and disposed of in an environmentally safe manner.

7. A gravity column (7 cm x 15 cm) was packed with 60-230 mesh silica gel. Elution was effected with 10% ethyl acetate in petroleum ether.

8. Spectroscopic data are as follows: ^1H NMR (400 MHz, CDCl_3) δ : 1.68 (s, 3 H, cis- CH_3), 1.74 (s, 3 H, trans- CH_3), 2.20 (s, 3 H, ring CH_3), 3.17 (d, 2 H, $J = 7.0$, CH_2), 3.98 (s, 3 H, CH_3O), 3.99 (s, 3 H, CH_3O), 4.94 (t, 1 H, $J = 7.0$, $\text{C}=\text{CH}$); IR (neat) cm^{-1} : 2790, 1650, 1617, 1455, 1329, 1262, 1555, 1102, 1013.

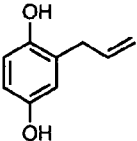
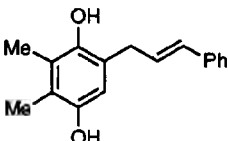
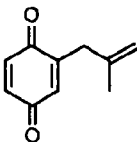
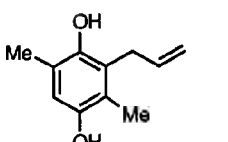
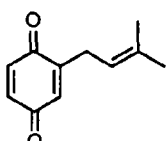
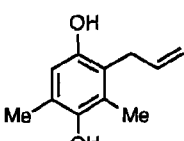
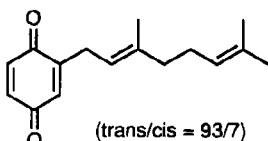
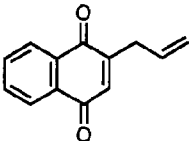
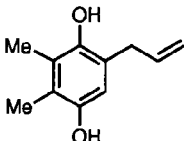
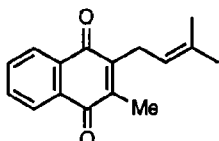
Waste Disposal Information

A chloroform solution of toxic tributyltin fluoride was placed in a round-bottomed flask equipped with a reflux condenser, and bromine (3 equiv per Bu_3SnF) was added all at once. After the mixture was stirred for 2-3 days at room temperature, aqueous sodium thiosulfate was added until the brown color of bromine disappeared. The aqueous layer containing inorganic tin compounds was disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

Ubiquinones are synthesized by the introduction of an isoprenyl side chain to the corresponding quinone or hydroquinone using several compounds: Lewis acid-isoprenyl alcohols,³ π -allylnickel bromides,^{4,5} isoprenyltrialkyltins,⁶ N-sulfinylamide-isoprenyl alcohols,⁷ amalgamated zinc-isoprenyl bromides,⁸ and Claisen rearrangement of isoprenyl aryl ethers.⁹ Among these procedures, the isoprenyltin method is superior to the others with respect to yield, simplicity of manipulation, and purity of product. This method can be also applied to the synthesis of the higher homologues of ubiquinone-*n* (*n*=2-10). In general, synthesis of allylated quinones or hydroquinones can be performed by the reaction with allylborane,¹⁰ π -allylnickel complexes,¹¹ allyltrimethylsilane,¹² or allyltrialkyltins.^{6,13,14} Direct allylation to the quinone is considered to be the best procedure compared with stepwise methods including protection/deprotection of quinone.¹⁵ The present method is applicable to a broad range of quinones and allylated trialkyltins to give the corresponding hydroquinone (or quinone after oxidation) in good to excellent yields. Several other examples are shown in the Table. In this reaction, boron trifluoride plays two roles: activation of the quinones resulting in 1,2-addition and acceleration of dienone-phenol rearrangement of the allylic group.⁸ In addition this method can be applied to the synthesis of many other polyprenylated quinones,^{6,13} including naturally occurring quinones, plastoquinone-*n*, phyloquinone (vitamin K₁), and menaquinone-*n* (vitamin K_{2(n)}). The polyprenyl side chain can be stereoselectively introduced into a quinone nucleus without formation of the corresponding chromanol or other side chain-cyclized products. Other methods of polyprenyl group introduction to quinones or their protected forms are known: a Friedel-Crafts alkylation,¹⁶ a free-radical alkylation,¹⁷ and coupling reactions with organometallic reagents including lithium,¹⁸ magnesium,^{19,20} and tin.²¹

TABLE
PREPARATION OF ALLYLATED QUINONES FROM QUINONES AND
ALLYLATED TRIBUTYLTINS

	Yield (%)		Yield (%)
	68		81
	45 ^a		90
	55 ^a		82
 (trans/cis = 93/7)	58 ^a		42 ^a
	72		78 ^a

^aIsolated after oxidation in ether with aqueous FeCl₃ solution.

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

Ubiquinone-1: p-Benzoquinone, 2,3-dimethoxy-5-methyl-6-(3-methyl-2-butenyl)- (8);
2,5-Cyclohexadiene-1,4-dione, 2,3-dimethoxy-5-methyl-6-(3-methyl-2-butenyl)- (9);
(727-81-1)

2,3-Dimethoxy-5-methyl-1,4-benzoquinone: p-Benzoquinone, 2,3-dimethoxy-5-methyl- (8); 2,5-Cyclohexadiene-1,4-dione, 2,3-dimethoxy-5-methyl- (9); (605-94-7)

Tributyl(3-methyl-2-butenyl)tin: Stannane, tributyl(3-methyl-2-butenyl)- (9);
(53911-92-5)

1-Chloro-3-methyl-2-butene: 2-Butene, 1-chloro-3-methyl- (8,9); (503-60-6)

Tributyltin chloride: Stannane, tributylchloro- (8,9); (1461-22-9)

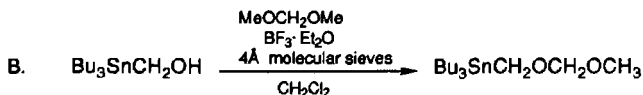
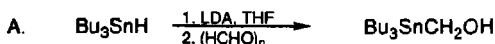
Boron trifluoride etherate: Ethyl ether, compd. with boron fluoride (BF₃) (1:1) (8);

Ethane, 1,1'-oxybis-, compd. with trifluoroborane (1:1) (9); (109-63-7)

Ferric chloride hexahydrate: Iron chloride, hexahydrate (8,9); (10025-77-1)

Potassium fluoride (8,9); (7789-23-3)

**A HYDROXYMETHYL ANION EQUIVALENT:
 TRIBUTYL[(METHOXYMETHOXY)METHYL]STANNANE
 (Stannane, tributyl[(methoxymethoxy)methyl]-)**



Submitted by Rick L. Danheiser,¹ Karen R. Romines,¹ Hiroo Koyama,¹

Stephen K. Gee,¹ Carl R. Johnson,² and John R. Medich.²

Checked by Darius J. Robinson and Amos B. Smith, III.

1. Procedure

A. (Tributylstannyl)methanol. A 500-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, an argon inlet adapter, and a 150-mL, pressure-equalizing, dropping funnel fitted with a rubber septum (Note 1). The flask is charged with 13.7 mL (0.098 mol) of diisopropylamine (Note 2) and 120 mL of dry tetrahydrofuran (Note 3), and then cooled with an ice-water bath while 58.4 mL (0.093 mol) of a 1.60 M solution of butyllithium in hexane (Note 4) is added dropwise via syringe over 15 min. After 30 min, a solution of 24.75 g (0.0850 mol) of tributyltin hydride (Note 5) in 50 mL of tetrahydrofuran is added dropwise via the addition funnel over 50 min. After 30 min, 3.57 g (0.119 mol) of paraformaldehyde (Note 6) is added in one portion, the ice bath is removed, and the heterogeneous yellow reaction mixture is stirred for 3 hr at room temperature. The resulting clear,

colorless solution is diluted with 500 mL of petroleum ether and washed with 300 mL of water. The aqueous phase is separated and extracted with 150 mL of petroleum ether, and the combined organic layers are washed with 200 mL of saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure using a rotary evaporator to afford approximately 30 g of (tributylstannyl)methanol as a colorless oil, which was used in the next step without further purification (Note 7).

B. Tributyl[(methoxymethoxy)methyl]stannane. A 1-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, an argon inlet adapter, and a rubber septum (Note 1). The flask is charged with the (tributylstannyl)methanol prepared in the previous reaction, 190 mL of dichloromethane (Note 8), 280 mL (3.16 mol) of dimethoxymethane (Note 9), and 50 g of powdered 4Å molecular sieves (Note 10). Boron trifluoride etherate (13.0 mL, 0.106 mol) (Note 11) is added dropwise over 2 min via syringe to the vigorously stirred reaction mixture, and the resulting orange suspension is stirred at room temperature for 13 hr, and then filtered through a 2-cm pad of Celite in a sintered-glass funnel. The filter cake is washed with 250 mL of dichloromethane, and the combined filtrates are washed with two 250-mL portions of saturated sodium bicarbonate solution. The combined aqueous layers are extracted with 250 mL of dichloromethane, and the combined organic phases are then washed with 250 mL of saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure using a rotary evaporator. The residual pale yellow oil (30 g) is dissolved in 20 mL of hexane and applied to 150 g of alumina (Note 12) packed in a 4.5-cm diameter column. The column is eluted with 1.3 L of 1% ethyl acetate-hexane (Note 13). The total eluant is concentrated at reduced pressure using a rotary evaporator, and the residual colorless oil is transferred to a 100-mL, round-bottomed flask and distilled through a 10-cm Vigreux column to furnish

23 g (74% overall yield based on tributyltin hydride) of tributyl[(methoxymethoxy)methyl]stannane as a colorless liquid, bp 117°C (0.34 mm) (Notes 14 and 15).

2. Notes

1. The glass components of the apparatus are immersed in a solution of 19.8 g of potassium hydroxide in 20 mL of water and 88 mL of ethanol for 20 min, dried overnight in a 150°C oven, and then assembled and maintained under an atmosphere of argon during the course of the reaction. This procedure removes traces of materials that otherwise can catalyze decomposition of the organotin reagents employed in the reaction.

2. Diisopropylamine was purchased from Aldrich Chemical Company, Inc. and distilled from calcium hydride before use.

3. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately before use.

4. Butyllithium was purchased from Aldrich Chemical Company, Inc. and titrated using the method of Watson and Eastham.³

5. Tributyltin hydride was freshly prepared by the method of Hayashi et al.⁴ Commercial tributyltin hydride (Aldrich Chemical Company, Inc.) can also be used, but in this case the yield of product is 5-7% lower.

6. Paraformaldehyde was obtained from Aldrich Chemical Company, Inc. and dried overnight in a desiccator over phosphorus pentoxide at 0.3 mm.

7. If desired, the product can be purified by column chromatography on 230-400 mesh silica gel (50 times by weight, elution with 5-10% ethyl acetate-hexane). (Tributylstannyl)methanol exhibits the following spectral properties: IR (film) cm^{-1} : 3320, 2970, 2940, 2880, 2860, 1465, 1440, 1380, 1360, 1345, 1295, 1255, 1185,

1155, 1075, 1045, 1025, 985, 875; ^1H NMR (300 MHz, CDCl_3) δ : 0.8-1.1 (m, 15 H), 1.2-1.7 (m, 13 H), 4.02 (d, 2 H, $J = 4.5$).

8. Dichloromethane was distilled from calcium hydride immediately before use.

9. Dimethoxymethane was obtained from Aldrich Chemical Company, Inc. and distilled from sodium before use.

10. Linde type 4Å molecular sieve pellets were crushed using a mortar and pestle and then dried under vacuum (0.3 mm) at 300°C^5 for 15 hr prior to use.

11. Boron trifluoride etherate ($\text{BF}_3\cdot\text{Et}_2\text{O}$) was purchased from Aldrich Chemical Company, Inc. and distilled at 20 mm from calcium hydride. The overall yield for the reaction is reduced by ca. 10% if less $\text{BF}_3\cdot\text{Et}_2\text{O}$ (1.1 equiv) or less dimethoxymethane (20 equiv) is employed.

12. EM Science 80-325 mesh alumina was used for this filtration.

13. Filtration of the crude product through alumina prior to distillation is necessary to obtain pure material. If the filtration step is omitted, product of only 85-90% purity is obtained.

14. The purity of this material was determined to be >99% by gas chromatographic analysis (0.25 mm x 30 m DB-1701 fused silica capillary column, 12 psi column pressure, 120°C for 2 min, 120 - 250°C at $10^\circ\text{C}/\text{min}$, then 250°C ; retention time 13.1 min).

15. The product has the following spectral properties: IR (film) cm^{-1} : 2970, 2930, 2880, 2770, 1465, 1420, 1395, 1380, 1345, 1295, 1245, 1205, 1150, 1100, 1040, 965, 930, 875, 730; ^1H NMR (250 MHz, CDCl_3) δ : 0.8-1.1 (m, 15 H), 1.2-1.7 (m, 12 H), 3.33 (s, 3 H), 3.74 (s, 2 H), 4.52 (s, 2 H); ^{13}C NMR (75 MHz, CDCl_3) δ : 8.9, 13.6, 27.3, 29.1, 54.9, 57.6, 99.4. Anal. Calcd for $\text{C}_{15}\text{H}_{34}\text{O}_2\text{Sn}$: C, 49.34; H, 9.39. Found: C, 49.68, H, 9.56.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

Hydroxymethyl anion equivalents play an important role as building blocks in the synthesis of complex organic compounds.⁶ Still⁷ has previously demonstrated the utility of $\text{Bu}_3\text{SnCH}_2\text{OCH}(\text{OEt})\text{CH}_3$ as a hydroxymethyl anion equivalent. The preparation of this reagent involves the addition of tributylstannyl lithium to paraformaldehyde followed by the protection of the resultant alcohol with α -chloroethyl ethyl ether. Transmetalation of the organostannane with one equivalent of butyllithium then furnishes an α -alkoxymethyl lithium reagent which adds to carbonyl compounds in good yield. Hydrolysis of the ethoxyethyl protective group provides the desired primary alcohols.

Like Still's reagent, tributyl[(methoxymethoxy)methyl]stannane incorporates an alcohol protective group that can be conveniently unmasked under mild acidic conditions. However, an advantageous feature of this MOM ether derivative is that, in contrast to Still's reagent, it is achiral. In many applications the introduction of an additional chiral center into synthetic intermediates is undesirable because of the complications associated with the manipulation, analysis, and purification of diastereomeric mixtures.

Methoxymethylation of alcohols is generally achieved through alkylation with chloromethyl methyl ether. The procedure described here for the preparation of $\text{Bu}_3\text{SnCH}_2\text{OCH}_2\text{OCH}_3$ avoids the use of the highly toxic chloromethyl ether by employing an acid-catalyzed acetal exchange reaction with dimethoxymethane for the

key protection step. Two related procedures have been developed for the methoxymethylation of (tributylstannyl)methanol based on this strategy.⁸⁻¹⁰ The protocol described here employs BF_3 -etherate and molecular sieves^{8,11} to promote the acetal exchange and results in a higher yield of product compared to the alternative Fujita procedure¹² that uses phosphorus pentoxide. In this fashion the title compound is obtained in excellent purity in 74% overall yield from tributyltin hydride. The accompanying procedure illustrates one application of this organotin compound as a hydroxymethyl anion equivalent.

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2. Department of Chemistry, Wayne State University, Detroit, MI 48202.
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10. The title compound has also been prepared by alkylations of (tributylstannyl)methanol with chloromethyl methyl ether (55% overall yield from paraformaldehyde): Sawyer, J. S.; Kucerovy, A.; Macdonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842.

11. Acetal exchange has previously been achieved using molecular sieves in combination with p-toluenesulfonic acid: Roelofsen, D. P.; Wils, E. R. J.; Van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 1141.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Tributyl[(methoxymethoxy)methyl]stannane: Stannane, tributyl[(methoxymethoxy)-methyl]- (11); (100045-83-8)

(Tributylstannyl)methanol: Methanol, (tributylstannyl)- (8,9); (27490-33-1)

Tributyltin hydride: Stannane, tributyl- (8,9); (688-73-3)

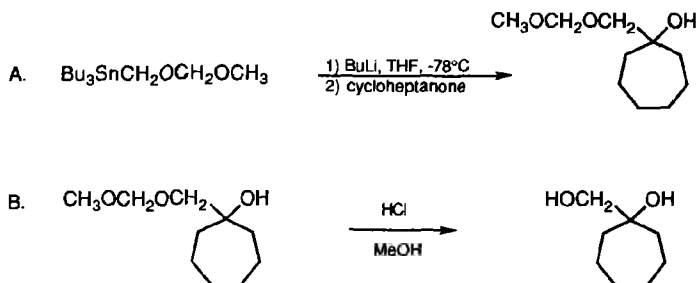
Paraformaldehyde (9); (30525-89-4)

Dimethoxymethane: Methane, dimethoxy- (8,9); (109-87-5)

Boron trifluoride etherate: Ethyl ether, compd. with boron fluoride (BF₃) (1:1) (8);

Ethane, 1,1'-oxybis-, compd. with trifluoroborane (1:1) (9); (109-63-7)

**PREPARATION AND USE OF (METHOXYMETHOXY)METHYLLITHIUM:
1-(HYDROXYMETHYL)CYCLOHEPTANOL
(Cycloheptanemethanol, 1-hydroxy-)**



Submitted by Carl R. Johnson,^{1a} John R. Medich,^{1b} Rick L. Danheiser,^{1c}

Karen R. Romines,^{1c} Hiroo Koyama,^{1c} and Stephen K. Gee.^{1c}

Checked by Darius J. Robinson and Amos B. Smith, III.

1. Procedure

A. 1-[(Methoxymethoxy)methyl]cycloheptanol. A 250-mL, three-necked, round-bottomed flask is equipped with a magnetic stirring bar, a rubber septum, an argon inlet adapter, and a thermometer port. The apparatus is flame dried under reduced pressure and evacuated; the vacuum is broken with argon. The flask is charged with tributyl[(methoxymethoxy)methyl]stannane (10.5 g, 28.7 mmol) (Note 1) and evacuated for 15 min; the vacuum is broken with argon. The flask is charged with 40 mL of dry tetrahydrofuran (Note 2), a low temperature thermometer is set into the flask and the solution is cooled to -78°C using a dry ice-acetone bath. A solution of butyllithium (2.5 M in hexanes, 11.2 mL, 28.0 mmol) (Note 3) is added via a syringe over a period of ~5

min while maintaining a reaction temperature below -60°C. Stirring is continued for no more than 5 min (Note 4), at which time cycloheptanone (2.70 g, 24.0 mmol) (Note 5) is added neat via a syringe. After the solution is stirred for 30 min at -78°C, the dry ice-acetone bath is removed and the reaction mixture is diluted with 40 mL of saturated aqueous ammonium chloride. The resulting mixture is stirred for 30 min and then extracted with three 40-mL portions of ethyl acetate. The combined organic layers are washed with 20 mL of saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure using a rotary evaporator to provide 12.8 g of crude product. The crude product is purified by flash chromatography on a 70-mm diameter column packed with 130 g of silica gel (Note 6) using 5% ethyl acetate/hexane to elute the tin by-products and 30% ethyl acetate/hexane to elute the title compound. The product fractions are combined and concentrated at reduced pressure using a rotary evaporator to provide 1-[(methoxymethoxy)methyl]cycloheptanol (4.1-4.3 g, 91-95% based on cycloheptanone) as a colorless liquid (Note 7).

B. 1-(Hydroxymethyl)cycloheptanol. To a 100-mL round-bottomed flask equipped with a stirring bar and a reflux condenser are added 1-[(methoxymethoxy)methyl]cycloheptanol (3.90 g, 20.7 mmol), methanol (50 mL), and hydrochloric acid (12.1 N, 0.75 mL). The reaction mixture is heated to 55°C for 1.5-2 hr (Note 8). After completion of the reaction, as indicated by TLC (Note 8), the reaction mixture is cooled to ambient temperature and carefully diluted with 35 mL of saturated aqueous sodium bicarbonate and stirred for 30 min. The methanol is removed under reduced pressure using a rotary evaporator and the remaining aqueous mixture is extracted with three 40-mL portions of ethyl acetate. The combined organic layers are washed once with 15 mL of saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, filtered, and concentrated at reduced pressure using a rotary evaporator to afford 2.9 g of crude product as a pale yellow oil. The crude product is

purified by flash chromatography on a 40-mm diameter column packed with 70 g of silica gel (Note 6), using 40% ethyl acetate-hexane to elute the product. The desired fractions are combined and concentrated under reduced pressure using a rotary evaporator to provide 1-(hydroxymethyl)cycloheptanol (2.3-2.4 g, 76-80% yield) as a white solid (mp 52-53°C) (Note 9).

2. Notes

1. The preparation of tributyl[(methoxymethoxy)methyl]stannane is described in an accompanying procedure, *Org. Synth.* **1992**, *71*, 133.

2. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately before use.

3. Butyllithium was purchased from Aldrich Chemical Company, Inc. and titrated using a solution of 2-butanol (1.0 M in p-xylene) with 1,10-phenanthroline as the end-point indicator.

4. In some cases the submitters have noticed that when the transmetalation mixture was allowed to stir for 15 min or more prior to addition of the carbonyl compound, the expected addition product was contaminated with material resulting from addition of butyllithium.

5. Cycloheptanone was purchased from Aldrich Chemical Company, Inc. and distilled under aspirator vacuum through a 6-in. Vigreux column prior to use.

6. Merck 230-400 mesh silica gel 60 was used for the column chromatography.

7. 1-[(Methoxymethoxy)methyl]cycloheptanol has the following spectral properties: IR (neat) cm^{-1} : 3460, 2930, 2860, 1460, 1445, 1405, 1212, 1198, 1150, 1112, 1042, 965, 920; ^1H NMR (400 MHz, CDCl_3) δ : 1.35-1.69 (m, 12 H), 2.40 (s, 1 H), 3.35 (s, 2 H), 3.35 (s, 3 H), 4.63 (s, 2 H); ^{13}C NMR (400 MHz, CDCl_3) δ : 22.3, 30.0,

37.6, 55.2, 74.6, 76.1, 97.0. Anal. Calcd for $C_{10}H_{20}O_3$: C, 63.80; H, 10.71. Found: C, 63.73; H, 10.82.

8. Progress of the reaction should be monitored periodically during the 2 hr to determine when the starting material is consumed in order to avoid unnecessary heating, which leads to the formation of by-products. TLC can be used: 50% ethyl acetate/hexane, silica gel stained with phosphomolybdic acid.

9. 1-(Hydroxymethyl)cycloheptanol has the following spectral properties: IR (KBr) cm^{-1} : 3370, 2920, 2858, 1465, 1445, 1375, 1341, 1230, 1190, 1075, 1029, 991, 961, 935, 920, 890, 850, 800, 710; 1H NMR (400 MHz, $CDCl_3$) δ : 1.3-1.8 (m, 12 H); 2.98 (s, 1 H), 3.38 (d, 2 H), 3.52 (t, 1 H); ^{13}C NMR (400 MHz, $CDCl_3$) δ : 22.4, 30.2, 37.2, 69.6, 76.0. Anal. Calcd for $C_8H_{16}O_2$: C, 66.63; H, 11.18. Found: C, 66.35; H, 11.39.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

The utility of α -alkoxyorganostannanes as precursors to α -alkoxyorganolithiums has been demonstrated by several groups.² Primary α -alkoxyorganostannanes^{2d-g} have been used as hydroxymethyl anion equivalents.³ Direct hydroxymethylation of carbonyl compounds was achieved by Seebach and Meyers,⁴ who treated tributylstannylmethanol with two equivalents of butyllithium (BuLi) to produce the dianion of methanol. The dianion added to carbonyl compounds to give diols directly.

The usefulness of this method, however, is limited because of the instability of the reagent and the moderate yields of addition products. Still prepared tributyl[(ethoxy)(methyl)methoxy]stannane and (benzyloxymethyl)tributylstannane.^{2e} These compounds, upon treatment with one equivalent of BuLi, gave α -alkoxyorganolithiums, which added in high yields to carbonyl compounds to provide monoprotected diols. The former reagent results in the introduction of a new chiral center and the latter results in a protected diol that must be unmasked by hydrogenolysis. The related "MOM" reagent described here was foreseen as fulfilling a need for an acid-sensitive protecting group that would not introduce new diastereomers.

Tributyl[(methoxymethoxy)methyl]stannane in tetrahydrofuran readily transmetalates with BuLi and the resulting (methoxymethoxy)methylolithium adds in high yield to carbonyl compounds, providing monoprotected diols.²⁹ The reagent can also be added in a conjugate fashion to enones, albeit in moderate yield,²⁹ using the copper methodology of Fuchs and Hutchinson.⁵ Deprotection of the alcohol can be achieved in high yield by simple acid hydrolysis.⁶

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 5. Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1987**, *109*, 4930.
 6. For other conditions for hydrolysis of methoxymethyl ethers, see: Greene, T. W.; Wuts, P. G. M. "Protective Groups In Organic Synthesis", 2nd ed.; Wiley: New York, 1991; p. 17.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(Methoxymethoxy)methyl lithium: Lithium, [(methoxymethoxy)methyl]- (12); (115384-62-8)

1-(Hydroxymethyl)cycloheptanol: Cycloheptanemethanol, 1-hydroxy- (10); (74397-19-6)

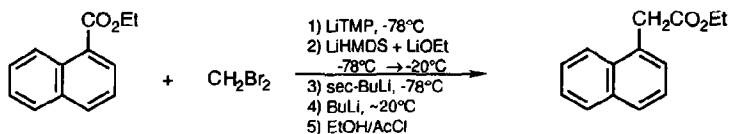
1-[Methoxymethoxy)methyl]cycloheptanol: Cycloheptanol, 1-[(methoxymethoxy)methyl]- (12); (115384-52-6)

Tributyl[(methoxymethoxy)methyl]stannane: Stannane, tributyl[(methoxymethoxy)methyl]- (11); (100045-83-8)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)

Cycloheptanone (8,9); (502-42-1)

**ETHYL 1-NAPHTHYLACETATE: ESTER HOMOLOGATION
VIA YNOLATE ANIONS
(1-Naphthaleneacetic acid, ethyl ester)**



Submitted by Rajarathnam E. Reddy and Conrad J. Kowalski.¹

Checked by Chang Y. Hong and Larry E. Overman.

1. Procedure

A. Preparation of lithium 2,2,6,6-tetramethylpiperidide (LiTMP). An oven-dried, 500-mL, round-bottomed flask, equipped with a magnetic stirring bar, nitrogen inlet, and septum, is filled with a nitrogen atmosphere and charged via syringe with 40.5 mL (33.9 g, 0.240 mol) of 2,2,6,6-tetramethylpiperidine (Note 1) and 250 mL of anhydrous tetrahydrofuran (Note 2). The rapidly stirred solution is cooled with an ice bath and 88.0 mL (0.220 mol) of 2.5 M butyllithium in hexanes (Note 3) is added via syringe over a 20-min period. This solution of lithium 2,2,6,6-tetramethylpiperidide is stirred with continued ice bath cooling for a period of about 30 min while the next reaction is readied.

B. In situ lithiodibromomethane preparation/addition. An oven-dried, 2-L, round-bottomed flask with three vertical necks, containing 20.0 g (0.100 mol) of ethyl 1-naphthoate (Note 4), is equipped with a 2-1/2 x 3/4-inch, egg-shaped magnetic stirring bar (Note 5), a -100°C to +50°C thermometer (Note 6) and a rubber septum.

The apparatus is flushed with nitrogen and a nitrogen atmosphere is maintained throughout the reaction using a nitrogen bubbler system that allows pressure release. The flask is charged through the septum (via syringe) with 200 mL of anhydrous tetrahydrofuran and 15.5 mL (38.3 g, 0.220 mol) of dibromomethane (Note 1). The thermometer (in a side neck) is adjusted so that the bulb is submerged when the liquid is stirred. The flask is immersed almost to the necks in a dry ice-acetone bath using about 2 L of acetone, and the contents are stirred vigorously for good heat transfer.

The lithium tetramethylpiperidide solution from Part A is cooled with a dry ice-acetone bath. When the solution of ethyl 1-naphthoate and dibromomethane has cooled to -74°C or below (internal solution temperature), addition of the dry ice-acetone cooled solution of lithium tetramethylpiperidide is begun. Addition is made via a double-ended (16 gauge) needle over a 40 to 50-min period using a slight positive nitrogen pressure in the 500-mL flask (Note 7). During this time, the addition rate is slowed or stopped as needed to maintain the reaction temperature below -67°C .

C. Preparation of lithium hexamethyldisilazide(LiHMDS)/lithium ethoxide. As the addition of Part B above is progressing, an oven-dried, 500-mL, round-bottomed flask, equipped with a magnetic stirring bar, nitrogen inlet, and septum, is filled with a nitrogen atmosphere and charged via syringe with 42.1 mL (32.2 g, 0.200 mol) of 1,1,1,3,3,3-hexamethyldisilazane (Note 1), 5.9 mL (4.6 g, 0.100 mol) of absolute ethanol, and 160 mL of anhydrous tetrahydrofuran. The rapidly stirred solution is cooled with an ice bath and 120 mL (0.300 mol) of 2.5 M butyllithium in hexanes is added via syringe over a 20-min period. The resulting solution of lithium hexamethyldisilazide and lithium ethoxide is stirred with continued cooling for a period of about 30 min and is then cooled with a dry ice-acetone bath (Note 8).

D. Base and butyllithium addition. Ten minutes after the addition of lithium tetramethylpiperidide to the main reaction is complete, the cold (ca. -70°C) solution of

lithium hexamethyldisilazide and lithium ethoxide is added (via a double-ended needle) over a 15 to 20-min period, while maintaining the reaction mixture temperature below -65°C . Five minutes after the addition is complete, the dry ice-acetone cooling bath is removed and the reaction mixture is allowed to warm. When the internal temperature of the solution has reached -20°C (after about 15 min), the reaction mixture is again cooled with a dry ice-acetone bath (Notes 9, 10). When the internal reaction temperature has reached -70°C or below, 308 mL (0.400 mol) of 1.3 M sec-butyllithium in cyclohexane (Note 11) is added via syringe over a 30 to 40-min period so that the internal temperature is maintained below -60°C . Five minutes after the addition is complete, the dry ice-acetone cooling bath is removed and the reaction mixture is allowed to warm. After the internal temperature has gradually reached ca. -10°C (Note 12), the reaction mixture is warmed to 20°C with a $\sim 25^{\circ}\text{C}$ water bath. A solution of butyllithium (80 mL, 0.200 mol) in hexanes is then added using a syringe pump over a 30 to 40-min period while the internal temperature is maintained between 20 - 25°C (Notes 13, 14). The reaction mixture is then allowed to stir for 30 min at room temperature (Note 15).

E. Quench and purification. While the butyllithium addition is taking place, an acidic ethanol quench solution is prepared in a 3-L, two-necked, round-bottomed flask, equipped with a mechanical stirrer and a 250-mL, pressure-equalizing dropping funnel. The flask is charged with 1 L of absolute ethanol and the funnel with 250 mL of acetyl chloride. The ethanol is stirred rapidly and the flask is cooled with an ice bath as the acetyl chloride is added over a 30-40-min period and then the cooling bath is removed and stirring is continued for 20-30 min. After the main reaction mixture has been stirred for 30 min at room temperature, it is cooled with a dry ice-acetone bath. The acidic ethanol solution is cooled with an ice bath and the cold, main reaction mixture is quenched by addition (via a double-ended needle) into the rapidly stirred, cold, acidic ethanol solution over a 3 to 3.5 hr period (Note 16).

After the quench is complete, the mixture is diluted with 2 L of ether and washed in a separatory funnel with 1.25 L of aqueous 10% hydrochloric acid. The aqueous layer is reextracted with a 2-L portion of ether. The combined ethereal layers are washed with 1.25 L of saturated brine solution and dried over anhydrous magnesium sulfate. After filtration and removal of solvent using a rotary evaporator there remains 26 g of crude product as a reddish-brown oil. Distillation of this material under reduced pressure through an unpacked, 2-inch distillation apparatus affords 17.3 g (81%) of ethyl 1-naphthylacetate as a yellow liquid, (bp 134-138°C, 0.2 mm) (Notes 17, 18).

2. Notes

1. 2,2,6,6-Tetramethylpiperidine, dibromomethane (99%) and 1,1,1,3,3,3-hexamethyldisilazane (98%) were purchased from Aldrich Chemical Company, Inc., and used without further purification. Use of less hindered secondary amines (such as diisopropylamine) in place of tetramethylpiperidine results in lower yields because of the formation of carboxamide by-products.

2. Reagent grade tetrahydrofuran was freshly distilled under nitrogen from a purple solution of sodium and benzophenone.

3. Solutions of butyllithium in hexanes and sec-butyllithium in cyclohexane were purchased from the Aldrich Chemical Company, Inc. It is recommended that only freshly opened bottles or extremely well protected solutions be used as the presence of lithium butoxide in partially decomposed bottles results in formation of the corresponding butyl ester as an undesired by-product.

4. Ethyl 1-naphthoate was purchased from Lancaster Synthesis, Inc., P.O. Box 1000, Windham, NH 03087, and used without purification. The checkers found that the purity of the ester was 95% by capillary GC analysis.

5. Good stirring is important to the success of this reaction, in order to provide efficient heat transfer during the addition of lithium tetramethylpiperidide and sec-butyllithium. The 2-1/2 x 3/4 inch stirring bar used is available from Aldrich Chemical Company, Inc.

6. The submitters recommend calibrating the thermometer to ca. -78°C when immersed in a dry ice-acetone bath. The thermometer used for these runs (Catalog #Z11,011-6) was purchased from Aldrich Chemical Company, Inc. Three different thermometers (two Fisher 15-035 and one Ertco X7048) were found that read from -86°C to -96°C when immersed in a dry ice-acetone bath! The checkers used a digital thermometer, model 450-ATT, purchased from OMEGA Engineering, Inc., Stamford, CT 05907.

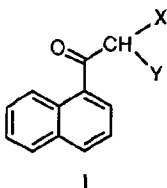
7. At a very low temperature the lithium tetramethylpiperidide solution may become too thick for smooth addition. If that occurs, the dry ice-acetone cooling bath is either partially or completely removed for a short period until addition can take place. The checkers warmed this mixture to -20°C to -10°C (whereupon it became a clear solution) prior to addition.

8. While it is important for all ester substrates that lithium hexamethyldisilazide be added before warming in order to avoid yield loss, the addition of lithium ethoxide (LiOEt) is specific for the naphthyl ester and is not generally necessary (see Discussion). Thus for other esters the ethanol can be omitted in this step and the amount of butyllithium can be reduced to 0.20 mol.

9. The reaction mixture turns from a yellow-orange color to a dark brown/black during the warming process, at ca. -35° to -25°C.

10. It is helpful to withdraw about a 0.20-mL aliquot of the reaction mixture after the warming-recooling process, to quench it in about 1.5 mL of a 1:5 mixture of acetyl chloride and absolute ethanol, and then to add about 1 mL of ethyl acetate and 0.5 mL of water. The mixture is shaken and most of the organic layer is transferred via pipette

to a tube containing anhydrous magnesium sulfate for drying. GC analysis of this material (at a convenient time) on a 50 m x 0.32 mm i.d. capillary column of cross-linked methylsilicone, at 40 psi of pressure for the helium carrier gas, and at a temperature raised from 100°C to 300°C at a rate of 15°C/min should show no remaining starting ester (ret. time = 6.5 min); instead it should show dibromo ketone **1a** (X = Br, Y = Br) at a ret. time = 9.0 min, monobromo ketone **1b** (X = H, Y = Br) at a ret. time = 7.7 min and monochloro ketone **1c** (X = H, Y = Cl) at a ret. time = 7.1 min (resulting from halogen exchange during the quench) in a ratio of about 3.9:4.2:1.



11. Use of butyllithium in place of sec-butyllithium at this point results in formation of some α -butylated ester by-product later upon warming, while use of sec-butyllithium in greater excess results in formation of methyl ketone **1d** (X, Y = H) in the final product.

12. *Caution: A pressure buildup can occur on this scale if the reaction mixture is warmed from -78°C to -10°C too rapidly and if the nitrogen inlet/pressure release system has very narrow constrictions. The initial warming is best done without a bath and takes about 15 min.*

13. The internal temperature is maintained between 20°C to 25°C during the addition with a cold water bath.

14. For non-aromatic esters, this addition can be carried out more conveniently by adding the butyllithium over 5-10 min (without cooling) once the internal

temperature has reached -20°C, and then warming to room temperature using a 20-25°C bath. For ethyl 1-naphthoate, however, addition of butyllithium at a lower temperature, or too quickly at a higher temperature, results in formation of ca. 3.2% of methyl ketone **Id** (X = Y = H). This lowers the yield and this compound is difficult to separate from the product.

15. It is wise to remove, quench, and analyze an aliquot from the reaction (as described in Note 10). At this point there should be no dibromo ketone **la** (X, Y = Br, ret. time = 9.0 min) or monobromo ketone (X = H, Y = Br, ret time = 7.7 min), but instead a strong peak for product at a ret. time = 6.8 min. If any monobromo or dibromo ketone is present in the 30-min aliquot, a longer time should be allowed for stirring at room temperature and/or slightly more butyllithium should be added.

16. It is important to quench the reaction *into* the acidic ethanol. If the quench solution is added to the reaction mixture, very little product is obtained.

17. The pot material in this distillation is rather viscous and tends to bump, so good stirring and extra care should be employed to avoid this problem. A low-boiling fraction (0.67-0.78 g, 95-133°C, 0.2 mm) is collected that is mostly a mixture of hydrocarbons and ethyl 1-naphthylacetate (ca. 1% yield). More than 90% of the product distills at 134-138°C, 0.2 mm. For the final few drops of product the bath temperature must be raised by 15-20°C, resulting in a slight rise in product boiling point; however, all the remaining distillate obtained is desired product.

18. G/C analysis (as in Note 10) of the final product, shows a single peak with retention time of 6.8 min. This material has the following spectral properties: IR (neat) cm^{-1} : 2981, 1730, 1598, 1512, 1445, 1174, 792, 780; ^1H NMR (CDCl_3) δ : 1.19 (t, 3 H, $J = 7.0$), 4.04 (s, 2 H), 4.13 (q, 2 H, $J = 7.1$), 7.39-7.51 (m, 4 H), 7.76 (dd, 1 H, $J = 2.4$, 7.1), 7.84 (d, 1 H, $J = 7.9$), 7.98 (d, 1 H, $J = 8.3$).

Waste Disposal Information

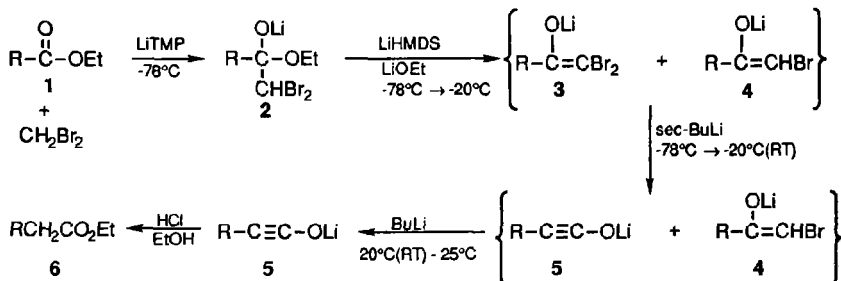
All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

This procedure illustrates a general method for the direct homologation of common esters, that represents a convenient, safer alternative to the classical Arndt-Eistert approach. Ethyl 1-naphthylacetate was selected for this demonstration since its preparation via the classical procedure has appeared previously in *Organic Syntheses*,² thus offering a direct comparison. In the earlier work, 1-naphthoyl chloride was prepared from the corresponding acid and converted using diazomethane to 1-(diazocetyl)naphthalene. Preparation of multigram quantities of hazardous diazomethane was required, and the 1-(diazocetyl)naphthalene produced was a severe skin irritant that had to be recrystallized in order to achieve the desired overall yield. Freshly prepared silver benzoate was then used to catalyze the Wolff rearrangement, providing the final ethyl 1-naphthylacetate in 78% overall yield (from the acid chloride). A modified Arndt-Eistert procedure using trimethylsilyldiazomethane has also been used to effect transformation of 1-naphthoyl chloride to ethyl 1-naphthylacetate in 66% yield on a 3-mmol scale.³

The current procedure starts with the ester, ethyl 1-naphthoate, and converts it into homologated product in 81% yield without isolation of any intermediates. Safe, commercially available materials are employed. Based on a recently published variation^{4a} of our original homologation methods,^{4b} it represents a general procedure applicable to esters 1 bearing aryl, alkenyl, alkynyl and primary, secondary or tertiary alkyl attachments R. Yields range from 67-90% (on a 25-mmol scale) and like the Arndt-Eistert sequence this procedure affords retention of stereochemistry for the

attachment R. It is also worth noting that this chemistry proceeds through the intermediacy of ynolate anions **5** that are useful for other processes,⁵ including the preparation of silyloxyacetylenes.⁶



Parts A and B of the procedure correspond to preparation of lithium tetramethylpiperide, and its use in the in situ preparation⁷ and addition of dibromomethyl lithium to the ester **1** producing tetrahedral intermediate **2**. In Part C a mixture of lithium hexamethyldisilazide and lithium ethoxide is prepared for addition in Part D to the solution of **2**. The silazide base serves to deprotonate the mono and dibromo ketones that are formed on initial warming of the reaction to -20°C , thus protecting them as the enolate anions **4** and **3**. Addition of the *sec*-butyllithium in Part D effects the key metal-halogen exchange/rearrangement of **3** at -78°C , converting it to the ynolate anion **5** (and producing *sec*-butyl bromide that does not alkylate the ynolate anion on subsequent warming). Addition of butyllithium, also in Part D, provides a source of base (regenerated lithium tetramethylpiperide) to deprotonate enolate **4** at room temperature and initiate rearrangement to ynolate **5**. The Part E quench then affords final product **6**.

Two modifications were made to our general procedure,^{4a} specifically to suit the ethyl 1-naphthoate case in this preparation, that are not necessary for most other

compounds. For most ynolate anions, **5**, the inverse quench into acidic ethanol described here is sufficient to eliminate significant formation of dimeric products resulting from ynolate anion reaction with the ketene intermediate. In the naphthalene case, however, about 3% of dimeric material (which complicates the distillation) is formed, possibly because of tighter aggregation of the ynolate anions via π -stacking. This was eliminated by adding an equivalent of lithium ethoxide (Parts C and D) to provide more ethoxide as an internal nucleophile/aggregate companion to trap effectively all the ketene formed in the quench. This ethoxide is not generally required for other substrates (Note 8).

It was also found for the naphthalene case (and to a lesser extent for phenyl), that small amounts of metal-halogen exchange can take place between bromoenolate **4** and butyllithium at room temperature, affording about 3% of acetophenone after quench. Thus the butyllithium addition was carried out slowly enough at room temperature so that no buildup of butyllithium would occur; under these conditions, the lithium tetramethylpiperidide deprotonation of **4** was occurring sufficiently fast to generate tetramethylpiperidine and to protonate the butyllithium as it was being added. For non-aromatic R groups on **4**, this competitive metal-halogen exchange was not a problem and the butyllithium need not be added slowly at room temperature (Note 14).

Ethyl 1-naphthoate thus represents one of the more difficult homologation cases, requiring the two modifications above. For most other compounds these are unnecessary and the procedure can be simplified as noted. On untried compounds one should always test the chemistry first on a small (2 mmol) scale, monitoring the quenched aliquots (as in Notes 10 and 15) to ensure that minor adjustments to the stoichiometry are not needed (e.g., a larger excess of dibromomethyl lithium in the first step to consume all the starting ester and/or more butyllithium in the final step to deprotonate/rearrange all the bromoenolate **4**). No such changes have been required

for any of the esters that we have investigated to date,^{4a} however, indicating that this procedure represents a quite general method for the direct homologation of common esters.

1. Synthetic Chemistry Department, SmithKline Beecham Pharmaceuticals, P.O. Box 1539, King of Prussia, PA 19406.
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5. (a) Kowalski, C. J.; Haque, M. S. *J. Am. Chem. Soc.* **1986**, 108, 1325; (b) Kowalski, C. J.; Lal, G. S. *Tetrahedron Lett.* **1987**, 28, 2463.
6. Kowalski, C. J.; Lal, G. S.; Haque, M. S. *J. Am. Chem. Soc.* **1986**, 108, 7127.
7. This preparation is patterned after the in situ preparation of dibromomethylithium for addition to ketones using lithium dicyclohexylamide, as reported by Taguchi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, 96, 3010.

Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Ethyl 1-naphthylacetate: 1-Naphthaleneacetic acid, ethyl ester (8,9); (2122-70-5)

Lithium 2,2,6,6-tetramethylpiperide: Piperidine, 2,2,6,6-tetramethyl-,
lithium salt (9); (38227-87-1)

2,2,6,6-Tetramethylpiperidine: Piperidine, 2,2,6,6-tetramethyl- (8,9); (768-66-1)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)

Ethyl 1-naphthoate: 1-Naphthoic acid, ethyl ester (8); 1-Naphthalenecarboxylic acid,
ethyl ester (9); (3007-97-4)

Dibromomethane: Methane, dibromo- (8,9); (74-95-3)

Lithium hexamethyldisilazide: Disilazane, 1,1,1,3,3,3-hexamethyl-, lithium salt (8);

Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)-, Lithium salt (9); (4039-32-1)

1,1,1,3,3,3-Hexamethyldisilazane: Disilazane, 1,1,1,3,3,3-hexamethyl- (8);

Silanamine, 1,1,1-trimethyl-N-(trimethylsilyl)- (9); (999-97-3)

Lithium ethoxide: Ethyl alcohol, lithium salt (8); Ethanol, lithium salt (9); (2388-07-0)

sec-Butyllithium: Lithium, sec-butyl- (8); Lithium, (1-methylpropyl)- (9); (598-30-1)

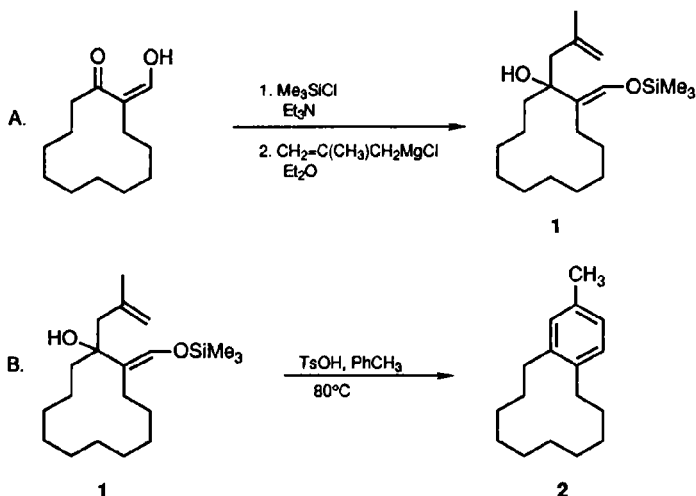
Acetyl chloride (8,9); (75-36-5)

Ethanol: Ethyl alcohol or ethanol (8); Ethanol (9); (64-17-5)

BENZOANNELATION OF KETONES:

3,4-CYCLODODECENO-1-METHYLBENZENE

(Benzocyclododecene, 5,6,7,8,9,10,11,12,13,14-decahydro-2-methyl-)



Submitted by Marcus A. Tius and G. S. Kamali Kannangara.¹

Checked by Annapoorna Akella and James D. White.

1. Procedure

A. *1-(2-Methylallyl)-2-(trimethylsiloxy)methylenecyclododecanol*. A dry, 2-L, three-necked, round-bottomed flask connected to a nitrogen bubbler and equipped with a mechanical stirrer with ground glass shaft and bearing a 100-mL pressure

equalizing dropping funnel and a septum inlet is charged with 45.4 g (1.89 mol) of magnesium turnings (Note 1) and flushed for 5 min with nitrogen. Anhydrous ether, 450 mL, (Note 2) is added and the flask is cooled to 0°C in an ice bath. Methallyl chloride, 64.6 mL (0.65 mol, Note 3) is added dropwise from the addition funnel to the stirred magnesium turnings during 45 min. (*Caution! The reaction is exothermic and care must be exercised to add the methallyl chloride at a moderate rate with adequate stirring and cooling of the reaction mixture*). During this time the reaction mixture turns to a gray heterogeneous slurry. Stirring is continued at 0°C for 1.5 hr and at 22°C for 1.5 hr.

In a separate, dry, 1-L, two-necked, round-bottomed flask fitted to a nitrogen bubbler and equipped with a magnetic stirring bar and a septum inlet is added a solution of 12.6 g (60.0 mmol) of 2-(hydroxymethylene)cyclododecanone (Note 4) in 500 mL of anhydrous ether. The stirred ethereal solution of the hydroxymethylene ketone is treated at 22°C with 33 mL of a freshly prepared mixture (1/1, v/v) of chlorotrimethylsilane and triethylamine (Note 5). An immediate reaction takes place with deposition of a white precipitate. The mixture is stirred thoroughly at 22°C for 15 min to insure complete conversion to the silyl enol ether.

The heterogeneous mixture of the silyl enol ether and triethylamine hydrochloride is transferred to the solution of the Grignard reagent at 0°C by means of a large-bore cannula (Note 6) during 15 min. The efficient transfer of the silyl enol ether is accomplished with the aid of nitrogen pressure. The flask containing the silyl enol ether is rinsed with 50 mL of ether that is transferred to the Grignard solution. Stirring at 0°C is continued for 15 min. The reaction is then quenched by slow addition of saturated aqueous sodium chloride solution until the reaction mixture becomes clear. (*Caution! The septa are removed from the flask in order to vent the pressure*). The solution is allowed to warm to 22°C and the ether layer is decanted from the magnesium salt and the unreacted magnesium. The residue is diluted with 100 mL of

saturated aqueous sodium chloride solution and extracted with ether (3 x 50 mL). The combined ether extracts are washed with brine (2 x 50 mL), dried over anhydrous magnesium sulfate and concentrated at reduced pressure. The product that is obtained is used in the next step without purification.

B. 3,4-Cyclododeceno-1-methylbenzene. A 1-L, two-necked, round-bottomed flask equipped with a reflux condenser, septum inlet, and a magnetic stirring bar is fitted to a nitrogen bubbler. The flask is charged with 200 mL of toluene (Note 7) and 4.6 g (24 mmol) of p-toluenesulfonic acid monohydrate (Aldrich Chemical Company, Inc.). The solution is warmed to 80°C in a heating mantle. Tertiary alcohol 1 from the preceding step is dissolved in 150 mL of toluene and transferred to the flask by cannula. The progress of the reaction can be monitored by silica gel TLC eluting with 20% ethyl acetate in hexane (Note 8). After 3 hr the reaction mixture is cooled to 22°C and washed with saturated aqueous sodium bicarbonate (2 x 100 mL). The aqueous phase is extracted with ether (4 x 100 mL) and the combined organic extracts are dried over anhydrous magnesium sulfate. The solvents are removed under reduced pressure and the residue is purified by flash column chromatography on silica gel, eluting with hexane. The benzoannulated product is obtained as a pale yellow oil in 86% overall yield (12 g; Note 9).

2. Notes

1. Magnesium turnings (98%) from Aldrich Chemical Company, Inc. were used after drying in a beaker at 110°C overnight. The Grignard reaction took place without need of an initiator.

2. Reagent grade ether was dried by distillation under argon from a purple solution of sodium benzophenone ketyl.

3. Methallyl chloride (obtained from Aldrich Chemical Company, Inc.) was distilled (bp 71-72°C) from phosphorus pentoxide prior to use.

4. See, Ainsworth, C. *Org. Synth., Coll. Vol. IV* **1963**, 536 and Woodward, R. B.; Pachter, I. J.; Scheinbaum, M. L. *Org. Synth., Coll. Vol. VI* **1988**, 590. The following modified procedure was used: To a 1-L, three-necked, round-bottomed flask equipped with a septum inlet, mechanical stirrer, nitrogen inlet, and pressure-equalizing dropping funnel was added 3.0 g (92 mmol) of sodium hydride (obtained from Aldrich Chemical Company, Inc.). The mineral oil was removed from the sodium hydride by washing with hexane. Ether was added (250 mL) and the reaction mixture cooled to 0°C. A mixture of 14 g (77 mmol) of cyclododecanone (obtained from Aldrich Chemical Company, Inc.) and 6.8 mL (85 mmol) of ethyl formate (obtained from Aldrich Chemical Company, Inc., and distilled from phosphorus pentoxide) in 75 mL of ether was added through the dropping funnel over 45 min. Next 4 mL of methanol was cautiously added. After 30 min the reaction became heterogeneous. Further addition of 4 mL of methanol allowed stirring to take place. The reaction mixture was then stirred for 4 hr at 0°C. The cooling bath was removed and stirring was continued for 8 hr at 23°C. The reaction was worked up by collecting the light yellow solid and dissolving it in 150 mL of water. The aqueous layer was washed once with ether to remove unreacted ketone and residual mineral oil. Careful acidification with 1 N hydrochloric acid to pH 6 was followed by extraction with ether (6 x 50 mL). The ether extracts were washed with brine (2 x 50 mL), dried (MgSO₄) and concentrated to produce 11.5 g of the hydroxymethylene ketone, which was used in the next step without purification. The spectrum was as follows: ¹H NMR (300 MHz, CDCl₃) δ: 1.30-1.39 (m, 12 H), 1.50-1.58 (br m, 2 H), 1.78-1.80 (br m, 2 H), 2.26 (t, 2 H, J = 6.9), 2.35 (t, 2 H, J = 7.5), 8.58 (d, 1 H, J = 3.6).

5. Chlorotrimethylsilane (obtained from Aldrich Chemical Company, Inc.) and triethylamine (obtained from Aldrich Chemical Company, Inc.) were mixed in equal

volumes in dry, stoppered tubes. These were centrifuged briefly and the supernatant was transferred through a septum by syringe.

6. A suitable cannula was made by filing the ends of a 45-cm long aluminum tube of 2-mm internal diameter to points.

7. Reagent grade toluene (obtained from Fisher Scientific Company) was degassed with a nitrogen stream.

8. The reaction was most easily monitored by noting the disappearance of the highly uv absorbing unsaturated aldehyde intermediate at $R_f = 0.41$ (20% ethyl acetate in hexane eluant).

9. The physical properties are as follows: ^1H NMR (300 MHz, CDCl_3) δ : 1.39-1.44 (m, 8 H), 1.51-1.54 (m, 4 H), 1.65-1.76 (m, 4 H), 2.29 (s, 3 H), 2.62 (t, 4 H, $J = 7.5$), 6.93-7.09 (m, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ : 20.95, 22.84, 22.85, 25.54 (two peaks overlap), 26.25, 26.30, 28.93, 29.29, 29.89, 29.98, 126.52, 129.45, 130.21, 134.91, 137.86, 140.74; IR (neat) cm^{-1} : 2940, 2880, 1510, 1475, 1450, 830, 810; mass spectrum m/e 230 (M^+ , 82%), 215 (4%), 173 (8%), 159 (20%), 145 (50%), 119 (100%), 105 (42%), 91 (20%), 40 (37%).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

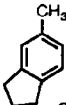
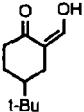
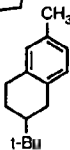
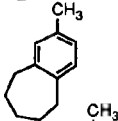
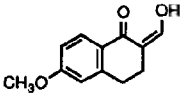
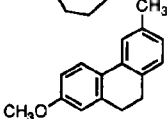
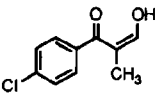
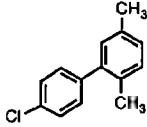
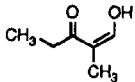
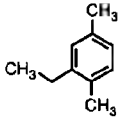
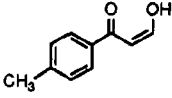
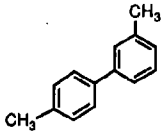
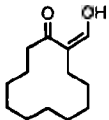
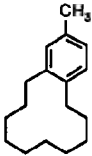
This preparation describes a highly practical and efficient method for the benzoannulation of ketones. The classical approach to the synthesis of aromatic

23°C for 12 hr with pyridinium tosylate in benzene.² This is an extraordinarily mild procedure for an aromatic annelation. The method is not limited to the preparation of methyl-substituted aromatics. By using benzylmagnesium bromide instead of methyl Grignard reagent, a naphthalene can be appended onto the ketone.³ Similarly, phenanthrenes³ and m-terphenyls⁴ can be obtained conveniently and in high yield. In the absence of a cation-stabilizing group at C-2 of the Grignard reagent, the yield for cyclization is diminished.⁵ A similar effect has been noted in related work.⁶ Unsubstituted, benzoannelated products are nevertheless accessible from cyclization of the adducts of [2-(trimethylsilyl)-2-propenyl]magnesium chloride.⁵

Several related methods for benzoannelation have been reported.⁷ Most provide aromatic sulfides or phenols that require additional manipulation. The present method provides convenient and highly efficient access to structurally diverse benzoannelated products. The ease of the reactions, the high yields, and the convenience recommend its use.

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TABLE
BENZOANNELATION OF KETONES

Entry	2-Hydroxymethylene ketone	Product	Overall yield (%)
1			52
2			76
3			79
4			74
5			66
6			89
7			65
8			86

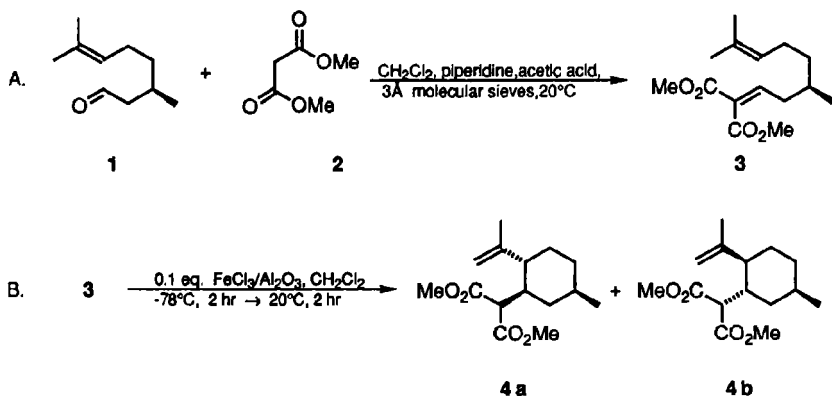
Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

3,4-Cyclododaceno-1-methylbenzene: Benzocyclododecene,
5,6,7,8,9,10,11,12,13,14-decahydro-2-methyl- (11); (81857-28-5)
Methallyl chloride: 1-Propene, 3-chloro-2-methyl- (8,9); (563-47-3)
2-(Hydroxymethylene)cyclododecanone: Cyclododecanone, 2-(hydroxymethylene)-
(9); (949-07-5)
Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)
p-Toluenesulfonic acid monohydrate (8); Benzenesulfonic acid,
4-methyl-, monohydrate (9); (6192-52-5)

**DIASTEREOSELECTIVE FORMATION OF TRANS-1,2-DISUBSTITUTED
CYCLOHEXANES FROM ALKYLIDENEMALONATES BY AN
INTRAMOLECULAR ENE REACTION: DIMETHYL (1'R,2'R,5'R)-
2-(2'-ISOPROPENYL-5'-METHYLCYCLOHEX-1'-YL)-PROPANE-
1,3-DIOATE**

**(Propanedioic acid, [5-methyl-2-(1-methylethenyl)cyclohexyl]-,
dimethyl ester, [1R-(1 α ,2 β ,5 α)]-)**



Submitted by L. F. Tietze and U. Baifuss.¹

Checked by David Rawson and Albert I. Meyers.

1. Procedure

A. *Methyl (5R)-2-(methoxycarbonyl)-5,9-dimethyldeca-2,8-dienoate*, **3**.² A dry, 250-mL, two-necked, round-bottomed flask, equipped with a magnetic stirring bar, calcium chloride drying tube, and rubber septum, is charged with 50 mL of dry

dichloromethane (Note 1), R-citronellal **1** (Note 2, 15.4 g, 18.0 mL, 100 mmol), dimethyl malonate, **2** (Note 3, 14.5 g, 12.5 mL, 110 mmol) and 3 Å molecular sieves (Note 4, 9.0 g). To the vigorously stirred mixture, piperidine (Note 5, 0.86 g, 1.00 mL, 10.0 mmol) and acetic acid (Note 6, 0.63 g, 0.6 mL, 10.0 mmol) are added simultaneously by syringes within a few seconds at room temperature. The reaction mixture is stirred for 30 min, another portion of molecular sieves (Note 4, 9.0 g) is added, and stirring is continued for another 2 hr (Note 7). After the solvent is removed on a rotary evaporator at 25°C, the resulting slurry is diluted with 30 mL of diethyl ether and the resulting mixture is filtered with suction using a Büchner funnel.

The residue is washed with diethyl ether (4 x 30 mL), and the combined organic layers are washed with water (3 x 30 mL), 1 N hydrochloric acid (3 x 30 mL), saturated sodium bicarbonate solution (3 x 30 mL), water (30 mL), and brine (3 x 30 mL), and finally dried over anhydrous sodium sulfate. Filtration and removal of the solvent on a rotary evaporator at 25°C yields 24.1-25.5 g (90-95%) of the Knoevenagel product as a colorless oil. The crude product is pure enough to be used in the ene reaction. An analytically pure sample of **3** (Note 8) is obtained by column chromatography (SiO₂) (Note 9) with petroleum ether/acetone, 98:2. Compound **3** is acid and base sensitive and should be stored under argon in a freezer.

*B. Dimethyl (1'R,2'R,5'R)-2-(2'-isopropenyl-5'-methylcyclohex-1'-yl)propane-1,3-dioate, 4a.*² A dry, 500-mL, three-necked, round-bottomed flask, equipped with a circular magnetic stirring bar, two rubber septa, and a three-way stopcock connected to an argon line and a vacuum line, respectively, is charged with ferric chloride on alumina (Note 10, 9.25 g, 9.50 mmol of ferric chloride). An argon atmosphere is established in the reaction flask by repeated cycles of evacuation and refilling with argon. Through use of a syringe, 210 mL of dry dichloromethane is added to the reaction flask. Under a positive argon stream, one rubber septum is replaced by a thermometer (-110°C to +30°C) and the other rubber septum is replaced by an argon-

flushed, pressure-equalizing dropping funnel sealed with a rubber septum and charged with a solution of **3** (25.5 g, 95.0 mmol) in 40 mL of dry dichloromethane (Note 1). The reaction flask is cooled to -78°C and the solution of **3** in dichloromethane is added dropwise over a period of 30-45 min with stirring at this temperature. Stirring is continued for 2 hr at -78°C and the mixture is allowed to warm to room temperature during 2 hr by taking away the dry ice-acetone bath. The solvent is removed on a rotary evaporator and the remaining brown slurry is treated with diethyl ether (50 mL); the resulting suspension is then filtered with suction using a Büchner funnel. The residue is washed with four portions of diethyl ether (50 mL) and the combined organic layers are washed with water (50 mL), saturated sodium bicarbonate solution (50 mL), 1 N hydrochloric acid (50 mL), water (50 mL), and brine (50 mL). The ethereal phase is dried over anhydrous sodium sulfate, filtered, and concentrated on a rotary evaporator to give 24.9 g (98%) of crude **4a/4b** as a yellowish oil in a 98.8:1.2 ratio. (The checkers determined the composition of **4a/4b** to be 97.4-97.8/2.6-2.2 by GC/MS.) The oil is purified by short path distillation under reduced pressure to yield 17.1-19.7 g 71-77%) of **4a/4b** as a clear, colorless, analytically pure liquid (Note 11). Analytically pure samples of **4a/4b** can also be obtained by flash column chromatography of the crude material on SiO_2 (Note 12) with diethyl ether/petroleum ether, 1:4) in 87% yield.

2. Notes

1. Dichloromethane is freshly distilled from phosphorus pentoxide or calcium hydride.

2. (R)-Citronellal purchased from Aldrich Chemical Company, Inc., Dragoco, Holzminden, or Takasago, Perfumery Co., Ltd., Tokyo was used as received. (R)-Citronellal can also be synthesized from pulegone with ee > 99%.³ The optical purity

of citronellal can be determined by GLC after conversion to the acetal of (-)-(2R,4R)-pentanediol⁴ or by HPLC of the amide of citronellic acid and (R)-(+)-1-(1-naphthyl)ethylamine.⁴ The chemical purity was checked by TLC. We are grateful to Dr. Brunke, Dragoco, Holzminden, Dr. Kumobayashi, Takasago, Tokyo and Dr. Nürrenbach, BASF, Ludwigshafen for gifts of (+)- and (±)-citronellal.

3. Dimethyl malonate was purified by distillation.

4. Molecular sieves (3 Å) were finely ground and dried under reduced pressure at 100°C for 24 hr prior to use.

5. Piperidine was purified by distillation prior to use.

6. Acetic acid was purified by distillation.

7. The final stirring period can be shortened to 1 hr if an additional 0.6 mL of acetic acid and 1 mL of piperidine are added at this point.

8. The physical properties of **3** are as follows: R_f 0.51 (ether/hexane, 1:1); HPLC 3.4 min (Nucleosil CN-10; ether/hexane, 1:2; flow 1.5 mL/min); IR (film, cm^{-1}): 1730, 1645, 1260, 1225, 1060; UV λ_{sh} 210 (4.13); ^1H NMR (100 MHz, C_6D_6) δ : 0.78 (d, 3 H, $J = 6.5$, 5- CH_3), 0.94-1.46 (m, 3 H, 5-H, 6- H_2), 1.53 (s br, 3 H, 10- H_3), 1.66 (s br, 3 H, 9- CH_3), 1.91 (q m, 2 H, $J = 7$, 7- H_2), 2.13 (multiplet centered, 2 H, 4- H_2), 3.39 (s, 3 H, OCH_3), 3.51 (s, 3 H, OCH_3), 5.10 (tm, 1 H, $J = 7$, 8-H), 7.06 (t, 1 H, $J = 8$, 3-H); ^{13}C NMR (20 MHz, C_6D_6) δ : 17.66 (C-10), 19.59 (5- CH_3), 25.81 (9- CH_3), 25.81 (C-7), 32.68 (C-5), 36.99 and 37.03 (C-4 and C-6), 51.69 and 51.81 (OCH_3), 124.89 (C-8), 129.80 (C-2), 131.25 (C-9), 148.48 (C-3), 164.20 (2-CO), 165.76 (C-1); MS m/z 268 (1, M^+), 237 (2, $\text{M}-\text{CH}_3\text{O}$), 136 (47, $\text{C}_{10}\text{H}_{16}$). Anal. Calcd for $\text{C}_{15}\text{H}_{24}\text{O}_4$: C, 67.14; H, 9.01. Found: C, 67.19; H, 9.03.

9. Compound **3** is isolated in 82% yield by flash chromatography on SiO_2 ; SiO_2 is Silica Woelm 32-63 active, Fa. Woelm Pharma, Eschwege or Aldrich Grade 951.

10. Iron(III) chloride on alumina is prepared as follows: A two-necked, round-bottomed flask is equipped with a circular magnetic stirring bar, a rubber septum, and an argon inlet adapter. The flask is flushed with argon and an argon atmosphere is maintained during the reaction. By use of a syringe the reaction flask is charged with dry dichloromethane (160 mL, Note 1). Iron(III) chloride from Merck AG, Darmstadt or Fluka Chemie AG, Buchs (10.0 g, 61.6 mmol) is added under argon and the suspension is vigorously stirred. Chromatography-grade neutral or basic alumina from Woelm Pharma, Eschwege (50.0 g) is added in small portions under argon. Stirring is continued for 1 hr to achieve homogeneous adsorption and the solvent is then removed on a rotary evaporator under reduced pressure at room temperature. The rotary evaporator is carefully flushed with argon. After drying under reduced pressure (0.01 atm) for 12 hr, 60 g of alumina-supported iron(III) chloride is obtained that can be stored under argon for several months without substantial loss of catalytic activity.

11. The physical properties of **4a/4b** are as follows: R_f 0.56 (diethyl ether/hexane, 1:1); GLC $t(4a)$ 16.88 min, $t(4b)$ 17.11 min (Chrompack 0.13 μ m CpSil 5, 0.32 mm x 25 m; 100°C, 5°C/min), **4a/4b** = 98.82: 1.18 $\pm$ 0.043, bp 128-129°C/0.5 mbar; $[\alpha]_D^{20}$ -34.6° (CH₃CN, c 1,2); IR (film, cm⁻¹) 3065, 1750, 1735, 1645, 1155, 1035, 1020, 895; ¹H NMR (200 MHz, CDCl₃) δ : 0.91 (d, 3 H, J = 6.5, 5'-CH₃), 0.95 (dq, 1 H, J = 3.5, 12, 4'-H ax), 1.11 (q, 1 H, J = 11.5, 6'-H ax), 1.24-1.57 (m, 2 H, 3'-H ax, 5'-H ax), 1.65 (multiplet centered, 3 H, 2''-CH₃), 1.57-1.94 (m, 3 H, 3'-H eq, 4'-H eq, 6'-H eq), 2.05 (dt, 1 H, J = 3.0, 11.5, 2'-H), 2.13 (tt, 1 H, J = 3.5, 11.5, 1'-H), 3.56 (d, 1 H, J = 3.5, 2-H), 3.73 (s, 6 H, OCH₃), 4.74 (multiplet centered, 1 H, 1''-H), 4.79 (m, 1 H, 1''-H); double resonance experiment, irradiation at δ 2.13 (1'-H), 3.56 (2-H), 4.79 (1''-H); significant change at δ 3.56 (s, 2-H) and 1.11 (t, 6'-H ax) 2.13 (1'-H), 1.65 (d, 2''-CH₃); ¹³C NMR (50 MHz, CDCl₃) of **4a/4b**, δ 18.96/19.36 (C-3''), 22.54/17.89 (5'-CH₃), 32.35/26.27 (C-3'), 32.73/27.32 (C-5'), 34.68/31.09 (C-4'), 36.59/33.47 (C-6'),

39.88/34.33 (C-1'), 48.68 (C-2'), 51.80 and 52.22 (OCH₃), 53.22/53.14 (C-2), 112.43/112.22 (C-1''), 147.52 (C-2''), 169.03 and 170.11/169.95 (C-1 and C-3); MS *m/z* 268 (4, M⁺), 136 (100, C₁₀H₁₆). Anal. Calcd for C₁₅H₂₄O₄: C, 67.14, H, 9.01. Found: C, 67.22; H, 9.07.

12. A mixture of **4a/4b** is isolated in 87% yield by flash chromatography on SiO₂; SiO₂ is Silica Woelm 32-63 active, Woelm Pharma, Eschwege or Aldrich Grade 951. Diastereomers **4a** and **4b** can be separated by chromatography, (diethyl ether/petroleum ether, 1:9) which, however, causes loss of material; it is also possible to separate the corresponding diols, that can be obtained by reduction with lithium aluminum hydride (LiAlH₄), by crystallization from diethyl ether.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

The tandem-Knoevenagel-ene reaction is a powerful tool to synthesize five- and six-membered carbocycles.^{2,5} The process is exemplified by the diastereoselective synthesis of **4a**. Compound **4a** has been obtained in both enantiomeric forms and as a racemate according to the procedure described here. The sequence includes the Knoevenagel reaction of citronellal, **1**, and dimethyl malonate, **2**, followed by the intramolecular ene cyclization of the chiral 1,7-diene **3** to yield the trans 1,2-disubstituted products **4a** and **4b**. Whereas the thermal cyclization of **3** at 180°C provides **4a** and **4b** in a ratio of only 89.7 : 10.3, the Lewis acid

promoted reaction can be performed at a lower temperature and shows a much higher diastereoselectivity.² If ferric chloride adsorbed on aluminum oxide is used, the reaction can be carried out at -78°C to give **4a** and **4b** in a ratio of 98:2 in 87% yield.² It should be stressed that FeCl₃/Al₂O₃ is employed as a catalyst using about 0.1 equiv. In the one reaction other Lewis acids such as diethylaluminum chloride (Et₂AlCl) and zinc bromide (ZnBr₂) may be used; however, they have to be added in at least equimolar amounts.² Compound **4a** has been used in the synthesis of terpenoid natural products.⁶

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Appendix

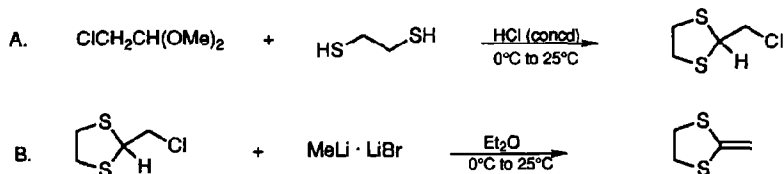
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Dimethyl (1'R,2'R,5'R)-2-(2'-isopropenyl-5'-methylcyclohex-1'-yl)-propane-1,3-dioate:
Propanedioic acid, [5-methyl-2-(1-methylethenyl)cyclohexyl]-, dimethyl ester,
[1R-(1 α ,2 β ,5 α)]- (12); (106431-81-6)

Methyl (5R)-2-methoxycarbonyl)-5,9-dimethyldeca-2,8-dienoate: Propanedioic acid,
(3,7-dimethyl-6-octenylidene)-, dimethyl ester, (R)- (12); (106431-76-9)
(R)-Citronellal: 6-Octenal, 3,7-dimethyl-, (R)-(+)- (8,9); (2385-77-5)

Dimethyl malonate: Malonic acid, dimethyl ester (8); Propanedioic acid, dimethyl ester
(9); (108-59-8)

2-METHYLENE-1,3-DITHIOLANE
(1,3-Dithiolane, 2-methylene-)



Submitted by Karl R. Dahnke and Leo A. Paquette.¹

Checked by M. Amornmarn, A. Focella, and D. L. Coffen.

1. Procedure

A. 2-Chloromethyl-1,3-dithiolane. A 500-mL, three-necked, round-bottomed flask equipped with a dropping funnel and magnetic stirrer is charged with 59.5 mL (0.71 mol) of 1,2-ethanedithiol (Note 1) and 50 mL of concd hydrochloric acid. This mixture is cooled to 0°C and 89 mL (0.78 mol) of chloroacetaldehyde dimethyl acetal (Note 2) is added via the dropping funnel over 2 hr (Note 3). After an additional 30 min, the ice bath is removed and the reaction mixture is stirred for 3 hr at room temperature. The resulting two-phase mixture is partitioned between dichloromethane (100 mL) and water (100 mL). The organic phase is separated and the aqueous phase is extracted with dichloromethane (100 mL). The combined organic layers are washed with water (100 mL), saturated sodium bicarbonate solution (100 mL), and brine (100 mL), then dried over magnesium sulfate. After removal of the solvent under reduced pressure, the viscous, colored residue (111 g) is subjected to bulb-to-bulb distillation using 500-mL and 250-mL collector bulbs and a 500-mL flask to hold the

crude product. The oven temperature is initially 20°C and is gradually increased to 120°C. Pressure is maintained at 0.25 mm. Initially *only* the bulb remote from the oven is cooled, using an acetone/dry ice bath. Solvent and volatile impurities are collected in this bulb. The product is then condensed in the bulb nearest the oven by placing a dry ice/acetone bath under this bulb after the higher boiling material begins to distill. The clear colorless oil thus obtained consists of fairly pure 2-chloromethyl-1,3-dithiolane (59.3-65.0 g, 54-59%) (Notes 4, 5 and 6).

B. 2-Methylene-1,3-dithiolane. A 1-L, three-necked, round-bottomed flask equipped with a pressure-equalizing dropping funnel, thermometer, magnetic stirrer, and nitrogen inlet is charged with 33.0 g (0.213 mol) of 2-chloromethyl-1,3-dithiolane and diethyl ether (400 mL) (Note 7). After the flask is flushed with nitrogen, the solution is cooled to 0°C. Methyl lithium-lithium bromide complex in diethyl ether (156 mL of 1.5 M solution, 0.235 mol) (Note 8) is transferred into the dropping funnel via cannula and added dropwise over 2 hr. After an additional 30 min, the ice bath is removed and the mixture is allowed to warm gradually to room temperature. After 2 hr at room temperature when methane evolution has ceased, the mixture is re-cooled to 0°C and quenched by dropwise addition of 50 mL of saturated ammonium chloride solution followed by sufficient water to just dissolve the salts. The organic layer is separated, washed with water (3 x 100 mL), saturated sodium bicarbonate solution (100 mL), and brine (100 mL), then dried over magnesium sulfate. The solvent is removed under reduced pressure and the residue is distilled through a short-path distillation apparatus (34-40°C at 1.0 mm) (Note 9) to give 20.6-21.6 g (82-86%) of 2-methylene-1,3-dithiolane as a light yellow oil (Note 10).

2. Notes

1. 1,2-Ethanedithiol was purchased from the Aldrich Chemical Company, Inc., and used without further purification.

2. Chloroacetaldehyde dimethyl acetal was obtained from the Elanco Company and used as received.

3. The addition was performed sufficiently slowly to maintain a temperature of 5-10°C.

4. During the thioketalization and distillation, thermal extrusion of HCl and isomerization to 2,3-dihydro-1,4-dithiin is observed² and the product of Step A typically contains ca. 10% of this impurity.

5. Storage of this material in a freezer is recommended.

6. Spectral characteristics are as follows: IR (CHCl₃) cm⁻¹: 3000, 2910, 1430, 1260; ¹H NMR (300 MHz, CDCl₃) δ: 3.22 (s, 4 H), 3.61 (d, 2 H, J = 7.2), 4.63 (t, 1 H, J = 7.2); ¹³C NMR (CDCl₃) δ: 38.36, 49.64, 54.23. Peaks arising from the 1,4-dithiin impurity appear at 3.18 and 6.08 ppm in the ¹H NMR.

7. Ether was distilled from sodium-benzophenone ketyl before use.

8. Methylolithium-lithium bromide complex was purchased from the Aldrich Chemical Company, Inc., and was titrated prior to use.

9. The receiver was cooled to -78°C and a small amount of triethylamine was added to the cold solution to stabilize the product against acid-catalyzed polymerization. As an added precaution, all glassware was base-washed prior to use.

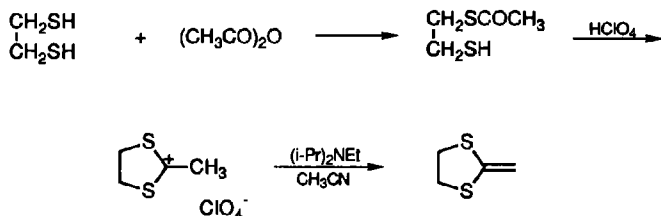
10. Spectral characteristics are as follows: IR (CHCl₃) cm⁻¹: 3000, 2930, 1675, 1575, 1525, 1425, 1285; ¹H NMR (300 MHz, CDCl₃) δ: 3.37 (s, 4 H), 5.13 (s, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ: 38.47, 99.60, 144.50. Peaks attributable to the 1,4-dithiin impurity carried through from Step A also appear in the ¹H NMR spectrum.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

Despite the latent reactivity of ketene thioacetals,^{3,4} some members of this class such as the title compound have been little studied, perhaps because of preparative inaccessibility. The only previously reported route to 2-methylene-1,3-dithiolane involves monoacetylation of 1,2-ethanedithiol, cyclization to 2-methyl-1,3-dithiolan-2-yl perchlorate, and exposure of this salt to diisopropylethylamine in acetonitrile.⁵



The process requires vast amounts of solvent, proceeds in low yield, and is plagued by the need to isolate and handle a potentially explosive intermediate.

Herein is described a much simpler dehydrohalogenation alternative that had been earlier applied successfully to the preparation of ketene acetals^{6,7} and 2-alkylidene-1,3-dithianes.⁸ This route appears not to have been examined for preparing the title compound because of an early report that 2-lithio-1,3-dithiolanes undergo ready fragmentative elimination to form ethylene and dithiocarbonate unlike

their stable 1,3-dithiane homologues.⁸ In point of fact, the loss of chloride ion from lithiated 2-chloromethyl-1,3-dithiolane is the kinetically-favored elimination reaction. Use of the present two-step procedure makes possible the safe, direct acquisition of 2-methylene-1,3-dithiolane in unlimited quantities.

The following *Organic Syntheses procedure*⁹ illustrates one of the uses of this reactive intermediate.

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

2-Methylene-1,3-dithiolane: 1,3-Dithiolane, 2-methylene- (9); (26728-22-3)

2-Chloromethyl-1,3-dithiolane; 1,3-Dithiolane, 2-(chloromethyl)- (11); (86147-22-0)

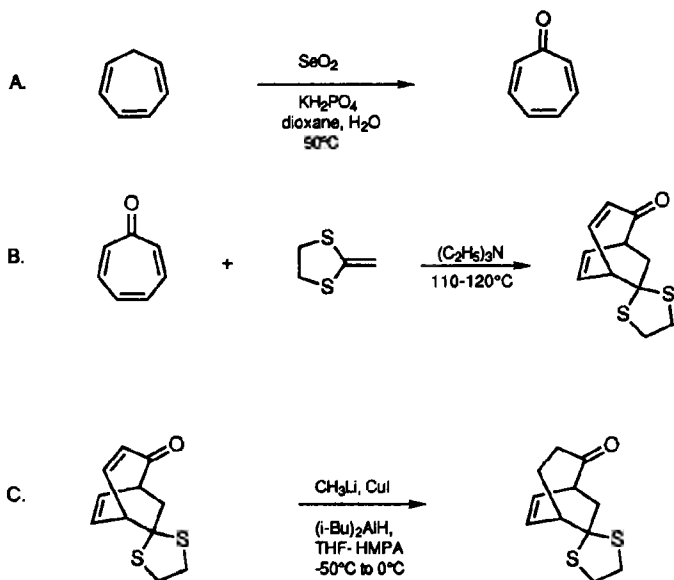
1,2-Ethanedithiol (8,9); (540-63-6)

Chloroacetaldehyde dimethyl acetal: Acetaldehyde, chloro-, dimethyl acetal (8);

Ethane, 2-chloro-1,1-dimethoxy- (9); (97-97-2)

Methylithium - lithium bromide complex: Lithium, methyl- (8,9); (917-54-4)

**INVERSE ELECTRON-DEMAND DIELS-ALDER CYCLOADDITION OF A
KETENE DITHIOACETAL. COPPER HYDRIDE-PROMOTED REDUCTION
OF A CONJUGATED ENONE. 9-DITHIOLANOBICYCLO[3.2.2]NON-
6-EN-2-ONE FROM TROPONE**



Submitted by Karl R. Dahnke and Leo A. Paquette.¹

Checked by Antonino Focella, Mittira Amornmarn, and David L. Coffen.

1. Procedure

A. Tropone. A 5-L, three-necked, Morton flask, equipped with a reflux condenser, thermometer, nitrogen inlet, and mechanical stirrer is charged with 81 g (0.59 mol) of potassium dihydrogen phosphate, 200 mL of water, and 2 L of p-dioxane. With vigorous mechanical stirring, 258 g (2.80 mol) of cycloheptatriene (Note 1) is added, followed by 318 g (2.87 mol) of selenium dioxide (Note 2). The mixture is heated to 90°C and maintained with vigorous stirring for 20 hr. After the black suspension is cooled to room temperature, 1 L of water is added and the mixture is filtered over Cellite (Note 3). The solution is divided into two halves and each is extracted with dichloromethane (2 x 1.5 L). Each organic extract is washed with saturated sodium bicarbonate solution (500 mL) and the solvent is removed under reduced pressure. The combined, crude, black oil is subjected to bulb-to-bulb distillation (20-110°C at 0.05 mm) with dry ice cooling. The resulting light brown liquid is fractionally redistilled (62-65°C at 0.25 mm) to give 147 g (50%) of tropone as a pale yellow oil (Note 4).

B. 9-Dithiolanobicyclo[3.2.2]nona-3,6-dien-2-one. A 50-mL, three-necked, round-bottomed flask, equipped with a reflux condenser, nitrogen inlet, and magnetic stirring bar is charged with 8.23 g (77.6 mmol) of tropone, 0.75 mL of triethylamine (Note 5), and 11.0 g (93.1 mmol) of 2-methylene-1,3-dithiolane (Note 6). After the system is flushed with nitrogen, the mixture is heated to 110-120°C for 10 hr. The resulting dark oil is cooled to room temperature and purified by column chromatography on silica gel (Note 7). Elution with petroleum ether (1 L) followed by dichloromethane affords 9-dithiolanobicyclo[3.2.2]nona-3,6-dien-2-one as an orange oil that solidifies (10.3 g, 59%), mp 56-58°C (Note 8).

C. 9-Dithiolanobicyclo[3.2.2]non-6-en-2-one. A 500-mL, three-necked, round-bottomed flask, equipped with an argon inlet, stirring bar, thermometer, and rubber

septum is charged with 0.80 g (4.2 mmol) of copper(I) iodide (Note 9) and 150 mL of dry tetrahydrofuran (Note 10). The resulting slurry is cooled to -50°C and treated in turn with 3.2 mL of 1.4 M methyllithium in ether (4.5 mmol), 40 mL of hexamethylphosphoramide (Notes 11 and 12), and 50 mL of a 1.0 M solution of diisobutylaluminum hydride in hexanes (Note 13), all via syringe. After 1.5 hr at -50°C, 7.4 g (33 mmol) of 9-dithiolanobicyclo[3.2.2]nona-3,6-dien-2-one (Note 14) in 30 mL of tetrahydrofuran is added over 10 min via syringe. The mixture is allowed to warm gradually to 0°C over a 4-hr period and quenched with 75 mL of 1.6 N hydrochloric acid. The organic layer is separated and the aqueous layer is extracted with ether (3 x 100 mL). The combined organic layers are washed with 1.6 N hydrochloric acid (75 mL), water (3 x 150 mL), and brine (150 mL), prior to drying over magnesium sulfate. Evaporation of the solvent under reduced pressure yields an orange oil which solidifies on standing for a short time (Note 15). The solid 9-dithiolanobicyclo[3.2.2]non-6-en-2-one thus obtained is vacuum dried to give 6.9 g (92%) of material, mp 68-71°C, as one spot on TLC, with no starting material detectable upon NMR analysis (Note 16).

2. Notes

1. Cycloheptatriene was purchased from the Aldrich Chemical Company, Inc., and was washed with 10% sodium hydroxide solution, dried over magnesium sulfate, and distilled prior to use.

2. Selenium dioxide was obtained from Alfa Products, Morton/Thiokol Inc. and used without purification.

3. The solid material containing selenium waste was placed in a container for heavy metal wastes and disposed of by a commercial service according to approved procedures.

4. Spectral characteristics are as follows: IR (CHCl_3) cm^{-1} : 3000, 1630, 1580, 1515, 1470, 1210; ^1H NMR (300 MHz, CDCl_3) δ : 6.88-7.11 (series of m, 6 H).

5. Triethylamine was distilled from calcium hydride prior to use.

6. 2-Methylene-1,3-dithiolane was prepared by the procedure of Dahnke and Paquette, *Org. Synth.* **1992**, *71*, 175.

7. The R_f for this adduct is 0.6 in CH_2Cl_2 . Its presence is clearly visible when anisaldehyde is employed as the staining agent.

8. The adduct exhibits the following spectral properties: IR (CHCl_3) cm^{-1} : 2930, 1665, 1603, 1380, 1165; ^1H NMR (300 MHz, CDCl_3) δ : 2.72 (d, 1 H, $J = 15.5$), 2.87 (dd, 1 H, $J = 6.8, 15.5$), 3.21-3.45 (m, 5 H), 3.66 (t, 1 H, $J = 7.7$), 5.77 (dd, 1 H, $J = 2.0, 11.1$), 6.13 (t, 1 H, $J = 7.9$), 6.60 (dt, 1 H, $J = 0.8, 7.6$), 6.92 (dd, 1 H, $J = 8.5, 11.1$); ^{13}C NMR (75 MHz, CDCl_3) δ : 40.2, 40.6, 42.9, 51.9, 52.1, 70.8, 126.5, 129.4, 139.4, 150.6, 196.3. A sample recrystallized from hexane afforded off-white crystals with mp 62-63°C. As an alternative to chromatography, the Diels-Alder adduct can be purified by pouring the cooled, crude product into 100 mL of ether and rinsing the dark viscous gum with additional ether (2 x 25 mL). The material obtained from evaporation of the combined ethereal extracts is then subjected to bulb-to-bulb distillation. After removal of the volatile impurities, the product distills during the ramping of the temperature from 110-165°C at 0.5 mm. This modification affords a comparable yield of adduct on a 6-fold scale.

9. Copper iodide was purified prior to use by the method of Kauffman.²

10. Tetrahydrofuran was distilled from sodium-benzophenone ketyl before use.

11. Hexamethylphosphoramide (HMPA) was distilled from calcium hydride and stored over molecular sieves before use.

12. Attempts were made to substitute other polar solvents for HMPA in this reduction. Under similar reaction conditions but with substitution of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone (DMPU) no reaction took place, and the starting

material was recovered unchanged. The slightly more polar 1,3-dimethyl-2-imidazolidinone (DMI) allowed reduction to take place, but with only 80% conversion to a mixture of 1,2- and 1,4-reduction products after 10 hr. With L-selectride in tetrahydrofuran (THF) at -78°C, 1,4-reduction was achieved in 30-60% yield alongside competitive 1,2-reduction.

13. Diisobutylaluminum hydride was purchased from the Aldrich Chemical Company, Inc. and used as received.

14. Before use, this material should be thoroughly dried by heating to 50°C under high vacuum to constant weight (1-2 hr).

15. The R_f of this product is 0.6 in CH_2Cl_2 . Anisaldehyde was employed as the staining agent.

16. Spectral characteristics are as follows: IR (CHCl_3) cm^{-1} : 2930, 2860, 1700, 1425; ^1H NMR (300 MHz, CDCl_3) δ : 1.82-1.94 (m, 1 H), 2.28-2.38 (m, 1 H), 2.52-2.70 (m, 3 H), 2.83-2.94 (m, 2 H), 3.10 (t, 1 H, $J = 7.3$), 3.22-3.48 (m, 4 H), 6.14 (t, 1 H, $J = 7.9$), 6.51 (t, 1 H, $J = 8.2$); ^{13}C NMR (75 MHz, CDCl_3) δ : 27.1, 38.1, 39.4, 39.8, 42.9, 46.8, 49.1, 69.9, 127.3, 137.3, 206.9. An analytical sample recrystallized from ether melts at 74-75°C. Anal. Calcd for $\text{C}_{11}\text{H}_{14}\text{OS}_2$: C, 58.37; H, 6.23; S, 28.33. Found: C, 58.32, H, 6.22; S, 28.63.

Waste Disposal Information

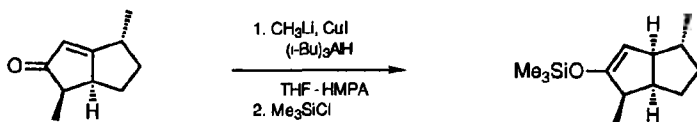
All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

Although examples of inverse electron-demand Diels-Alder reactions involving ketene thioacetals and α,β -unsaturated aldehydes, ketones, and esters abound,³ the formation of six-membered carbocyclic products is rarely encountered. Isoquinolinium salts and 4a-azoniaanthracenes are recognized as good 2π acceptors,⁴ but the use of positively charged reaction partners is not necessary as the condensation with tropone illustrates. An important advantage of such cycloadditions is their ability to distinguish two carbonyl groups from the outset. Furthermore, the example provided illustrates the regioselectivity with which carbon-carbon bond formation occurs.

The methodology employed for the oxidation of cycloheptatriene is based on an original report by Radlick⁵ as subsequently improved by Rigby and Wilson.⁶

The second stage of the procedure describes a method for the fully regiocontrolled saturation of conjugated double bonds in the presence of isolated pi bonds. The agent perhaps responsible for this discrimination is a coordinated form of copper hydride. Although "CuH" has been generated in several different ways, the diisobutylaluminum hydride-methyl copper-HMPA complex developed by Tsuda and Saegusa⁷ is especially attractive because of its quantitative capacity for 1,4-reduction and its ease of generation.⁸ This chemistry results in regiospecific enolate anion formation and permits ready trapping of these intermediates as illustrated below:⁹



Consequently, this mild, conjugate reduction may become a powerful tool in synthetic organic chemistry.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

Tropone: 2,4,6-Cycloheptatrien-1-one (8,9); (539-80-0)

Potassium dihydrogen phosphate: Phosphoric acid, monopotassium salt (9);
(7778-77-0)

Cycloheptatriene: 1,3,5-Cycloheptatriene (8,9); (544-25-2)

p-Dioxane (8); 1,4-Dioxane (9); (123-91-1)

Selenium dioxide: Selenium oxide (8,9); (7446-08-4)

Triethylamine (8); Ethanamine, N,N-diethyl- (9); (121-44-8)

2-Methylene-1,3-dithiolane: 1,3-Dithiolane, 2-methylene- (9); (26728-22-3)

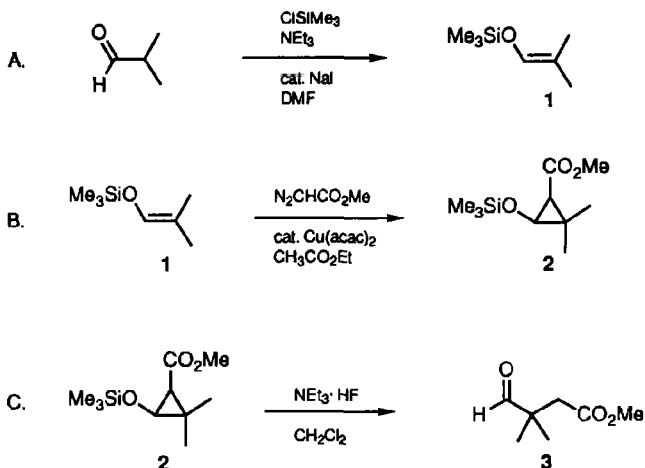
Copper(I) iodide: Copper iodide (8,9); (7681-65-4)

Methyl lithium: Lithium, methyl- (8,9); (917-54-4)

Hexamethylphosphoramide: Phosphoric triamide, hexamethyl- (8,9); (680-31-9)

Diisobutylaluminum hydride: Aluminum, hydrodiisobutyl- (8); Aluminum, hydrobis(2-methylpropyl)- (9); (1191-15-7)

**METHOXYCARBONYLMETHYLATION OF ALDEHYDES VIA
SILOXYCYCLOPROPANES: METHYL 3,3-DIMETHYL-4-OXOBUTANOATE
(Butanoic acid, 3,3-dimethyl-4-oxo-, methyl ester)**



Submitted by Hans-Ulrich Reissig, Ingrid Reichelt, and Thomas Kunz.¹

Checked by Lawrence Snyder and Albert I. Meyers.

1. Procedure

A. *2-Methyl-1-(trimethylsiloxy)propene* (**1**). A dry, 1-L, three-necked flask, equipped with an efficient mechanical stirrer, reflux condenser with nitrogen inlet, and a pressure-equalizing dropping funnel, is charged with 230 mL of dry dimethylformamide (Note 1), 7.5 g (50 mmol) of dry sodium iodide (Note 2), and 119 g (1.18 mol) of triethylamine (Note 3) under a nitrogen atmosphere.

Chlorotrimethylsilane (Note 4), 64.3 g (0.592 mol) and 36.0 g (0.500 mol) of freshly distilled isobutyraldehyde are added sequentially to this stirred mixture via the dropping funnel at room temperature. Under vigorous stirring the resulting mixture is heated to 120°C (oil bath temperature) for 8 hr, then cooled to room temperature and poured into 400 mL of saturated aqueous sodium bicarbonate (NaHCO_3) solution. The mixture is extracted with three 200-mL portions of pentane, the combined organic phases are washed four times with 60 mL of ice-cold 2 N hydrochloric acid (Note 5) and finally with 100 mL of saturated NaHCO_3 solution, dried with magnesium sulfate (MgSO_4), filtered, and the pentane is removed at atmospheric pressure to provide crude product (80 g). This material is carefully distilled at atmospheric pressure through a column packed with glass beads (30 cm). Silyl enol ether 1 is the fraction boiling at 94-108°C; the yield is 48.8 g (67%, Note 6).

B. Methyl 2,2-dimethyl-3-(trimethylsiloxy)-1-cyclopropanecarboxylate (2).
Caution: This step should be performed behind a safety shield. A 500-mL flask, equipped with a magnetic stirring bar and a reflux condenser that contains at its head a pressure-equalizing dropping funnel connected to a gas bubbler, is charged with 1.04 g (4.00 mmol) of copper(II) acetylacetonate [$\text{Cu}(\text{acac})_2$] (Note 7) and 28.8 g (200 mmol) of silyl enol ether 1. The suspension is heated to 90-100°C (oil bath temperature) and a solution of 24.0 g (240 mmol) of methyl diazoacetate (Note 8) dissolved in 250 mL of dry ethyl acetate (Note 9) is added dropwise within 3-4 hr (Note 10). After a short induction period, vigorous nitrogen evolution is observed and the suspension turns from blue to brownish-yellow. Addition of the diazo compound is regulated so that continuous liberation of nitrogen is observed at the gas bubbler. After the resulting black-brown suspension is cooled to room temperature, the solvent is removed on a rotary evaporator (bath temperature below 35°C). The residue is treated with 50 g of alumina (Note 11) and 100 mL of pentane; the slurry is filtered and placed on a column that contains 200 g of alumina. Elution with pentane is

accelerated by applying a slight pressure of nitrogen at the top of the column. Concentration of the colorless solution obtained (Note 12) provides crude **2** (55 g) that is distilled (bp 86-88°C, 12 mm) to give 35.0 g (81%, Note 13) of pure cyclopropane derivative **2** as a mixture of cis/trans isomers (Note 14).

C. Methyl 3,3-dimethyl-4-oxobutanoate (3). A 50-mL flask, connected to a gas bubbler and equipped with a magnetic stirring bar, is charged with 20 mL of dichloromethane (or tetrahydrofuran), 2.16 g (10.0 mmol) of siloxycyclopropane **2** and 3.64 g (30.0 mmol) of triethylamine hydrofluoride (NEt₃·HF) prepared in situ (Note 15). This mixture is stirred for 1 hr at room temperature (Note 16) and diluted with 20 mL of water. The aqueous phase is extracted with three 20-mL portions of dichloromethane. The combined organic phases are dried with magnesium sulfate, filtered, and concentrated on a rotary evaporator (bath temperature below 40°C). Crude product **3** is distilled with a Kugelrohr oven (oven temperature 105°C, 10 mm) to provide 1.26 g (87%) of pure **3** as a colorless liquid (Note 17).

2. Notes

1. Dimethylformamide (Aldrich Chemical Company, Inc.) was distilled from phosphorus pentoxide and stored over molecular sieves.

2. The procedure described is a slight variation of the published method.² We found addition of ca. 10% sodium iodide to be advantageous in terms of reaction times and yields. Sodium iodide was dried at 120°C/0.2 mm for 6 hr.

3. Triethylamine was distilled from calcium hydride (CaH₂) and stored over molecular sieves.

4. Chlorotrimethylsilane (obtained from Fluka Chemical Company or Janssen) was distilled from calcium hydride.

5. The washing process was performed until the aqueous phase was acidic to pH paper. The checkers found that gas pressure build-up was common, so the separatory funnel should be vented frequently during acidification.

6. The fraction boiling at 94-108°C was found to be ~99% pure by GLC and contained a trace of hexamethyldisiloxane. The impurity does not affect the outcome of the next step. The NMR spectrum was as follows: ¹H NMR (270 MHz, CDCl₃) δ: 0.14 (s, 9 H), 1.52 (s, 3 H), 1.57 (s, 3 H), 5.98 (m, 1 H).

7. Copper(II) acetylacetonate, as supplied by Dynamit Nobel or by other commercial sources, was used.

8. Methyl diazoacetate was obtained according to a procedure for ethyl diazoacetate (Searle, N.E. *Org. Synth., Coll. Vol. IV* 1963, 42). Although the experiments were usually performed with distilled methyl diazoacetate (bp 43°C at 25 mm, bath temperature below 60°C) without any problems, the cyclopropanation reaction described works equally well with undistilled diazo compound. If distilled diazo compound is desired, the submitters have stated that "a spatula of K₂CO₃ is added to the crude diazo ester to trap traces of acid and then distill behind a safety shield". The checkers did not evaluate this aspect of the procedure.

Crude methyl diazoacetate contains up to 20% of the solvent dichloromethane, which has to be taken into account when calculating the stoichiometry. The checkers had no problems in preparing, handling, and using undistilled methyl diazoacetate; however, it must be emphasized that this compound is a potential explosive and all operations should be performed behind an efficient safety shield.

9. Our first experiments were performed with benzene as solvent, which generally provides very good yields.³ Use of the less hazardous solvent ethyl acetate gives inferior yields if the silyl enol ether contains triethylamine. Ethyl acetate was distilled from potassium carbonate.

10. If the solution of methyl diazoacetate is dropped through the condenser the diazo compound is further diluted by the refluxing solvent. This simple technique diminishes formation of dimethyl fumarate and dimethyl maleate as side products.

11. Neutral aluminum oxide (activity III, Woelm) was used.

12. Siloxycyclopropane **2** is eluted very quickly. Final fractions contain dimethyl fumarate and maleate. If mixtures of **2** with these carbene dimers are obtained, the filtration through alumina has to be repeated.

13. Yields of 75-85% have been obtained in several experiments on this scale.

14. The cis/trans ratio is 25:75. The spectra are as follows: IR (CCl_4) cm^{-1} : 1728 (CO_2Me); ^1H NMR (270 MHz, CDCl_3) δ : 0.12 (s, 9 H, SiCH_3), 1.04, 1.15, 1.19, 1.30 (4 s, 6 H, 2- CH_3 of cis-**2** and trans-**2**), 1.35, 3.42 (2 d, $J = 7$, 0.25 H each, 1-H and 3-H of cis-**2**), 1.43, 3.60 (2 d, $J = 3$, 0.75 H each, 1-H and 3-H of trans-**2**), 3.63 (s, 3 H, CO_2CH_3). For ^{13}C NMR data, mass spectrum, and combustion analysis see reference 3.

15. The reagent was generated in situ by sequential addition of 1.63 mL of triethylamine trihydrofluoride (obtained from Riedel deHaan, Merck, or Aldrich Chemical Company, Inc.) and 2.80 mL of triethylamine to the solution of **2**. The procedure reported in reference 4 provides a reagent with an approximate stoichiometry of $\text{NEt}_3\cdot 2\text{HF}$ that can also be used for the purpose described.⁵

16. A short period of gas evolution is observed. This is probably fluorotrimethylsilane (Me_3SiF).

17. This procedure can be performed without any problems on a larger scale (2.6 g, 90% yield was obtained by checkers). However, aldehyde **3** is of limited stability and should be stored with exclusion of oxygen at low temperature. It is advantageous to generate only the amount of **3** required for subsequent reactions and to use it immediately. The physical properties are as follows: IR (CCl_4) cm^{-1} : 1739, 1730 (CO_2Me , CO); ^1H NMR (270 MHz, CDCl_3) δ : 1.13 (s, 6 H, 3- CH_3), 2.52 (s, 2 H,

CH₂), 3.63 (s, 3 H, CO₂CH₃), 9.53 (s, 1 H, CHO). Anal. Calcd for C₇H₁₂O₃: C, 58.32; H, 8.39. Found: C, 58.59; H, 8.77.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

This sequence illustrates a very general method for the synthesis of methyl γ -oxoalkanoates which are valuable intermediates in organic synthesis.^{3,6} The scope of the cyclopropanation reaction is very broad; only functional groups interacting with the carbenoid generated from methyl diazoacetate are not compatible. Use of Rh₂(OAc)₄ instead of Cu(acac)₂ as catalyst did not afford better yields.³ The cyclopropanation reaction has been performed with similar efficiency on scales from 4 mmol up to 500 mmol.

Silyl enol ethers derived from aldehydes (see Table, entries 1-5) or ketones (entries 6-9) can be used. If unsymmetrical ketones are used as starting material, the regiochemistry established at the silyl enol ether stage is cleanly transferred to the siloxycyclopropanes and eventually to the methyl γ -oxoalkanoates (entries 7-9). For some chiral silyl enol ethers, high stereoselectivities can be attained in the [2+1]-cycloaddition. Because of the very mild conditions for the ring opening step, using the only weakly acidic fluoride reagent, the stereoselectivity is transmitted to the γ -oxoalkanoate without accompanying epimerization (entry 9).^{5,7} This mild, ring-opening procedure that uses NEt₃·HF is essential for preparation of the β -formyl

esters as described in the procedure and for entries 1-5 in the Table. For simple ketone-derived products ring cleavage can also be effected with 2 N hydrochloric acid.⁵

The methyl γ -oxoalkanoates shown are not available by alternative methods with similar efficiency and flexibility. Although the reaction of enamines with alkyl α -bromoacetates proceeds well in some cases, yields are only moderate in many examples.⁸ A further drawback is that the methods for enamine generation lack the high degree of selectivity and mildness that is characteristic of the preparation of silyl enol ethers. Related alkylations of lithium enolates often afford low yields or polyalkylated products, and are in general very inefficient when aldehydes are utilized as the starting materials.⁹

An alternative method to prepare β -formyl esters uses different building blocks to assemble the 1,4-dicarbonyl system and is complementary in many cases.¹⁰ Base-catalyzed addition of nitromethane to α,β -unsaturated esters, followed by a variation of the Nef reaction, provides γ -dialkoxy-substituted esters. The scope of this sequence has not yet been explored. Another approach involves cuprate additions to norephedrine-derived 2-alkenyloxazolidines; this process allows small-scale synthesis of several β -formyl esters in optically active form (ee up to 95%).¹¹

A major advantage of the sequence presented here is that the aldehyde group is protected at the siloxycyclopropane stage, which allows convenient storage of this stable intermediate. Of equal importance is the valuable carbanion chemistry that can be carried out α to the ester function. Efficient substitution can be achieved by deprotonation with LDA and subsequent reaction with electrophiles.^{12,13,6} This process makes several α -substituted β -formyl esters available. Other ring opening variants of siloxycyclopropanes - mostly as one-pot-procedures - are contained in Scheme I. They underscore the high versatility of these intermediates for the synthesis of valuable compounds.⁶ Chiral formyl esters (see Table, entries 2-5) are of special

interest as starting materials for chelate-controlled synthesis of disubstituted γ -lactones.¹⁴

Scheme 1

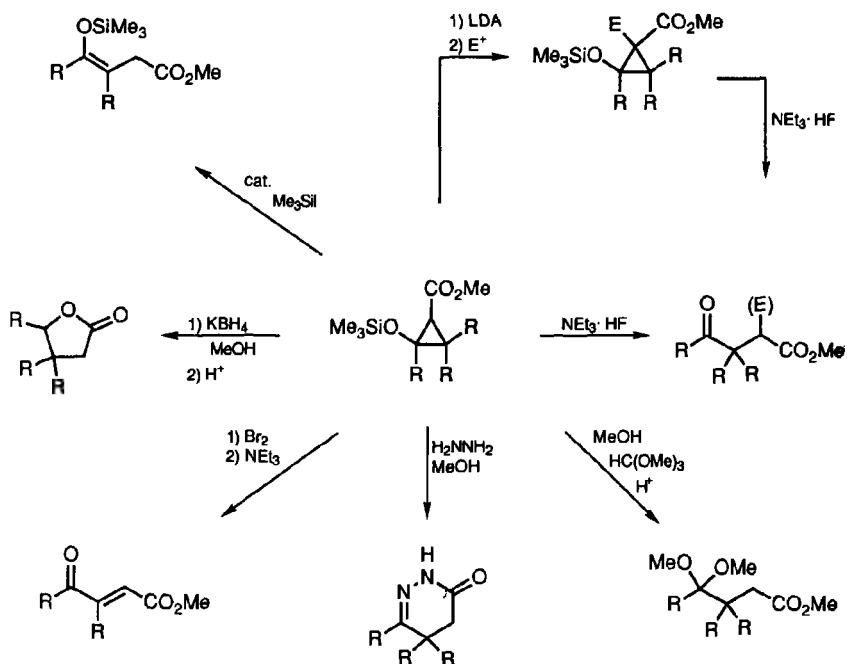


TABLE
SYNTHESES OF SILOXYCYCLOPROPANES AND γ -OXOALKANOATES

Entry	Silyl Enol Ether	Siloxy cyclopropane ^a (% yield)	γ -Oxoalkanoate (% yield)
1		 77%	 93%
2		 73% ^b	 91%
3	R = Me	80% ^b	84%
4	R = Et	65% ^b	71%
5	R = i-Prop	67% ^b	90%
	R = Ph		
6		 72%	 91%
7		 77%	 93%
8		 80%	 89%
9		 62%	 88% ^c

^aCis/trans isomers in all examples.

^bMixture of all four diastereomers.

^cTrans compound >95% (racemic mixture).

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

Methyl 3,3-dimethyl-4-oxobutanoate: Butanoic acid, 3,3-dimethyl-4-oxo-, methyl ester (9); (52398-45-5)

2-Methyl-1-(trimethylsiloxy)propene: Silane, trimethyl[(2-methyl-1-propenyl)oxy]- (8,9); (6651-34-9)

Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)

Isobutyraldehyde (8); Propanal, 2-methyl-, (9); (78-84-2)

Methyl 2,2-dimethyl-3-(trimethylsiloxy)-1-cyclopropanecarboxylate:

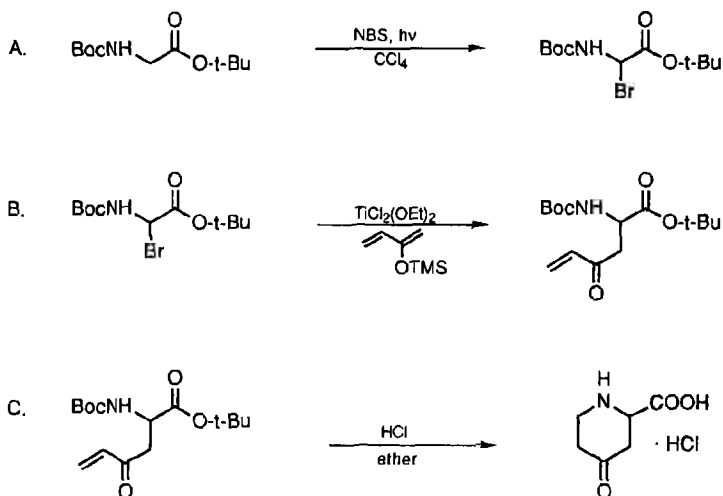
Cyclopropanecarboxylic acid, 2,2-dimethyl-3-[(trimethylsilyl)oxy]-, methyl ester (10); (77903-45-8)

Copper(II) acetylacetonate: Copper, bis(2,4-pentanedionato-O,O')- (9); (46369-53-3)

Methyl diazoacetate: Acetic acid, diazo-, methyl ester (8,9); (6832-16-2)

Triethylammonium fluoride: Triethylamine hydrofluoride (8); Ethanamine, N,N-diethyl-, hydrofluoride (9); (29585-72-6)

**TITANIUM-MEDIATED ADDITION OF SILYL DIENOL ETHERS TO
ELECTROPHILIC GLYCINE: A SHORT SYNTHESIS OF
4-KETOPIPECOLIC ACID HYDROCHLORIDE
(Pipelicolic acid, 4-oxo-, hydrochloride)**



Submitted by Clarisse Mühlemann, Peter Hartmann, and Jean-Pierre Obrecht.¹

Checked by Eugene Ho and David L. Coffen.

1. Procedure

A. 2-Bromo-N-Boc-glycine tert-butyl ester. In a 1-L, round-bottomed flask are placed 20.0 g (0.0865 mol) of N-Boc-glycine tert-butyl ester (Note 1) and 16.2 g (0.0912 mol) of N-bromosuccinimide (Note 2). Carbon tetrachloride (350 mL, Note 3)

is added, the flask is connected to a clean rotatory evaporator (Note 4) and the apparatus is flushed with argon. The flask is cooled, while being rotated, by means of a water bath and is irradiated with two 150-W tungsten lamps (Note 5) for 1 hr. The colorless solution becomes dark red and a precipitate forms. The suspension is filtered through a Schlenk tube and the carbon tetrachloride (CCl_4) is evaporated under reduced pressure. The remaining yellowish oil is employed in the next step without purification (Note 6).

B. *tert*-Butyl [1-(*tert*-butoxycarbonyl)-3-oxo-4-pentenyl]carbamate. The crude bromination product from the previous step is taken up in 240 mL of dry tetrahydrofuran (THF) (Note 7) and transferred to a 1000-mL flask equipped with a stirrer, thermometer, dropping funnel, and argon inlet. The solution is cooled to -78°C and a solution of 42 g (0.20 mol) of dichlorodiethoxytitanium $[\text{TiCl}_2(\text{OEt})_2]$ in 80 mL of dry THF (Note 8) is added at such a rate that the internal temperature does not exceed -72°C . When the addition is complete, the reaction mixture is stirred at -78°C for 10 min and then 24 g (0.170 mol) of 2-trimethylsiloxybutadiene (Note 9) in 100 mL of THF is added dropwise, causing only a slight increase in temperature (-72°C). The reaction mixture is allowed to warm to room temperature overnight and poured into 700 mL of ice-cooled, saturated sodium bicarbonate solution. After filtration through Celite, the aqueous phase is extracted with three 200-mL portions of ether. The combined organic layers are washed twice with water, dried over magnesium sulfate (MgSO_4), filtered, and concentrated. The remaining dark oil (29 g) is subjected to flash chromatography (20-cm column diameter, ether/hexane 1:3); 8.44–8.73 g (33–36%) (Note 10) of the product is obtained as a slightly yellowish oil (Note 11).

C. 4-Ketopiperic acid hydrochloride. *tert*-Butyl [1-(*tert*-butoxycarbonyl)-3-oxo-4-pentenyl]carbamate, 8.73 g (0.0308 mol), is dissolved in 280 mL of an ice-cooled, saturated solution of hydrogen chloride in ether. The solution is kept without stirring at room temperature overnight. The resulting suspension is filtered and the

filter cake is immediately washed with dry ether (Note 12). The washing with ether is repeated four times and, after drying under reduced pressure, 5.48 g (99%) of 4-ketopiperic acid hydrochloride is obtained as a colorless powder, mp 139-142°C dec (Note 13).

2. Notes

1. Boc-Glycine tert-butyl ester can be prepared by treatment of glycine tert-butyl ester hydrochloride (Aldrich Chemical Company, Inc.) with di-tert-butyl dicarbonate (Fluka Chemical Corporation) and triethylamine in THF.²

2. N-Bromosuccinimide was purchased from Fluka Chemical Corporation, recrystallized from water, and dried well in a vacuum desiccator.

3. Carbon tetrachloride is toxic and should only be handled in a well-ventilated hood.

4. The rotatory evaporator was washed with ethanol and ether. Bromination on a smaller scale can be carried out in a three-necked, round-bottomed flask with a thermometer, argon inlet, and stirring bar. External cooling with a water bath to keep the internal temperature between 15° and 20°C is important. The use of more concentrated solutions should be avoided, since dimerization instead of bromination becomes the dominant reaction.

5. The water bath was coated with aluminum foil in order to increase the efficiency of the irradiation.

6. TLC (ethyl acetate/hexane 1:3; vanillin/concd. H₂SO₄/heat) reveals complete consumption of the starting material and only small amounts of impurities. The crude product is stable for several weeks at -20°C under argon.²

7. THF was distilled from potassium and benzophenone.

8. Tetraethyl orthotitanate, 22.9 g (0.100 mol), (Fluka Chemical Corporation, bulb-to-bulb-distilled at 110-115°C/0.1 mm) is dissolved in 80 mL of dry THF. Titanium chloride (TiCl_4) (Fluka Chemical Corporation), 19.0 g (0.100 mol, distilled at 136°C/atmospheric pressure) was added dropwise while cooling with an acetone/dry ice bath to keep the temperature below 0°C. Alternatively, TiCl_4 may be added to a solution of $\text{Ti}(\text{OEt})_4$ (obtained from Aldrich Chemical Company, Inc.) in hexane at 0°C; the solvent is evaporated and replaced by THF.³

9. Trimethylsiloxybutadiene was purchased from Petrarch Systems, Inc., and employed without further purification. The checkers attempted to use the more stable triethylsiloxybutadiene without success.

10. In an experiment on one tenth the scale, the yield was 57%.⁴

11. The physical properties are as follows: $^1\text{H-NMR}$ (CDCl_3) δ : 1.44 (s, 18 H), 3.08 (dd, 1 H, $J = 4$ and 18), 3.28 (dd, 1 H, $J = 4$ and 18), 4.45 (m, 1 H), 5.48 (d, 1 H, $J = 8$, N-H), 5.91 (dd, 1 H, $J = 2$ and 10), 6.25 (dd, 1 H, $J = 2$ and 18), 6.34 (dd, 1 H, $J = 10$ and 18); IR (CHCl_3) cm^{-1} : 3430, 3000, 2980, 2930, 1740, 1720, 1710, 1630, 1500.

12. When the filter cake contains hydrogen chloride, it is very hygroscopic. It should therefore be covered immediately with dry ether after the ethereal hydrogen chloride solution has been aspirated.

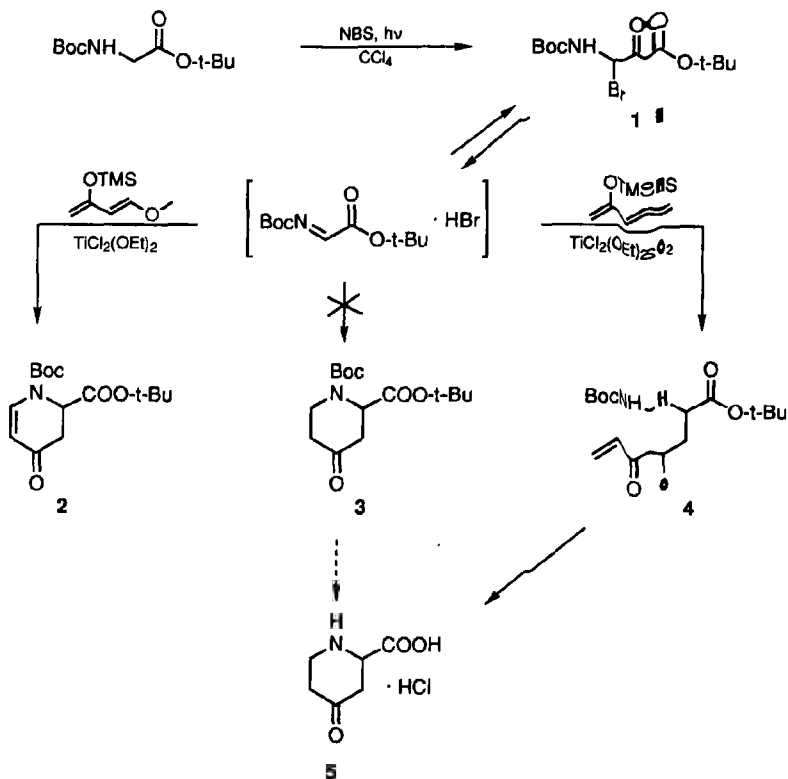
13. The physical properties are as follows: $^1\text{H NMR}$ (MeOD) δ : 3.05 (dt, 2 H, $J = 2$ and 6), 3.20 (dd, 1 H, $J = 7$ and 20), 3.29 (dd, 1 H, $J = 4$ and 20), 3.79 (t, 2 H, $J = 6$), 4.30 (dd, 1 H, $J = 4$ and 7); IR (nujol) cm^{-1} : 3300-2300 broad, 3060, 2960, 2920, 2860, 1740, 1725, 1600, 1570.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

N-Boc-2-Bromoglycine tert-butyl ester (**1**), introduced by Steglich and co-workers, is a versatile synthon for electrophilic glycine,⁵ an important tool in the synthesis of non-proteinogenic amino acids.



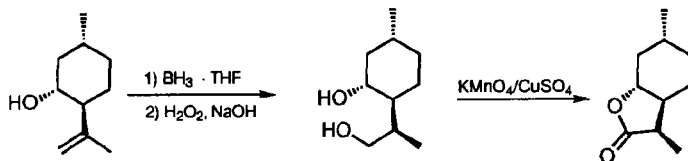
Elimination of HBr leads to an acylimino acetate that should be able to undergo an aza-Diels-Alder reaction with dienes to give pipercolic acid derivatives not readily accessible by other methods. Indeed, **1**, in the presence of $\text{TiCl}_2(\text{OEt})_2$, reacts with Danishefsky's diene between -78°C and room temperature to give the cyclic compound **2** in 72% yield. In a thermal reaction of 2-trimethylsiloxybutadiene with another electrophilic glycine equivalent, Jung and co-workers⁶ isolated a cyclic product of type **3**. Under the reaction conditions described here, the reaction product is not **3** but the enone **4**, which by itself is an interesting bifunctional intermediate. However, upon deprotection the anticipated ring closure takes place in a very clean fashion. Pure 4-ketopipercolic acid hydrochloride crystallizes out of the ethereal hydrogen chloride solution in quantitative yield, which illustrates the advantage of the use of **1** in amino acid synthesis, i.e., the ease of deprotection, often a critical step.

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

- 4-Ketopipicolinic acid hydrochloride: Pipicolinic acid, 4-oxo, hydrochloride, (11 (99979-55-2)
- 2-Bromo-N-Boc-glycine-tert-butyl ester: Acetic acid, bromo[[[(1,1-dimethylethoxy)-carbonyl]amino]-, 1,1-dimethylethyl ester, ($\pm$)-, (12); (111652-22-3)
- N-Boc-Glycine-tert-butyl ester: Glycine, N-[[[(1,1-dimethylethoxy)carbonyl]-, 1,1-dimethylethyl ester (12); (111652-20-1)
- N-Bromosuccinimide: Succinimide, N-bromo- (8); 2,5-Pyrrolidinedione, 1-bromo-, (9); (128-08-5)
- tert-Butyl [1-(tert-butoxycarbonyl)-3-oxo-4-pentenyl]carbamate: 5-Hexenoic acid, 2[[[(1,1-dimethylethoxy)carbonyl]amino]-4-oxo-, 1,1-dimethylethyl ester, (12); (117833-62-2)
- Dichlorodiethoxytitanium: Titanium, dichlorodiethoxy-, (8,9); (3582-00-1)
- 2-Trimethylsiloxybutadiene: Silane, trimethyl[(1-methylene-2-propenyl)oxy]-, (9); (38053-91-7)
- Glycine tert-butyl ester hydrochloride: Glycine, tert-butyl ester, hydrochloride (8); Glycine, 1,1-dimethylethyl ester, hydrochloride (9); (27532-96-3)
- Di-tert-butyl dicarbonate: Formic acid, oxydi-, di-tert-butyl ester (8); Dicarboxylic acid, bis(1,1-dimethylethyl)ester (9); (24424-99-5)
- Tetraethyl orthotitanate (Fluka Chemical Corporation), Titanium ethoxide (Aldrich Chemical Company, Inc.): Ethyl alcohol, titanium(4+) salt (8); Ethanol, titanium(4+) salt (9); (3087-36-3)
- Titanium chloride (9); (7550-45-0)

**A SELECTIVE, HETEROGENEOUS OXIDATION USING A MIXTURE OF
POTASSIUM PERMANGANATE AND CUPRIC SULFATE:
(3a*S*,7a*R*)-HEXAHYDRO-(3*S*,6*R*)-DIMETHYL-2(3*H*)-BENZOFURANONE
(2(3*H*)-Benzofuranone, hexahydro-3,6-dimethyl-,
[3*R*-(3α,3aβ,6β,7aα)]-)**



Submitted by Charles W. Jefford, Yun Li, and Ying Wang.¹

Checked by Timothy J. Watson and Leo A. Paquette.

1. Procedure

A. (-)-(1*R*,3*R*,4*S*,8*R*)-*p*-Menthane-3,9-diol. To a dry, 2-L, three-necked flask equipped with a gas outlet, an overhead stirrer, and a 500-mL pressure-equalizing dropping funnel with a gas inlet, is added a solution of 31 g (0.20 mol) of isopulegol (Note 1) in 550 mL of tetrahydrofuran (THF) (Note 2) under nitrogen. From the funnel, 230 mL of a 1.0 M diborane solution (Note 3) is added dropwise with stirring at room temperature at such a rate to insure that gas evolution is not violent. When the addition is complete, the clear solution is stirred for 3 hr at room temperature. The dropping funnel is removed and 100 mL of aqueous 3 N sodium hydroxide is added slowly; the solution is then warmed to 60°C on the steam bath for 2 hr. The gas outlet is replaced by a thermometer and the septum is replaced by another dropping funnel charged with 120 mL of aqueous 30% hydrogen peroxide and the reaction flask is

placed in an ice bath. Hydrogen peroxide is then added and the reaction temperature is maintained between 30-50°C by carefully controlling the rate of addition (the reaction is strongly exothermic at the beginning). When the addition is complete, the ice bath is removed and the reaction mixture is stirred at 50°C for 2 hr. The bulk of the THF is removed under reduced pressure and the residue is diluted with 200 mL of ether and washed with brine. The aqueous layer is extracted with two 50-mL portions of ether; the resulting extracts are combined and dried over anhydrous sodium sulfate for several hours and filtered. The filtrate is concentrated using a rotary evaporator. The resulting oil is dissolved in 100 mL of hot hexane, allowed to cool slowly, and stored at 0°C for 2 days. The supernatant mother liquor is decanted, 100 mL of fresh hexane is added, the crystalline mass is swirled for 2-3 min and the product is separated by filtration. After vacuum drying, 17.6 g (51%) of (-)-(1R,3R,4S,8R)-p-menthane-3,9-diol is obtained as colorless crystals, mp 105-107°C (Note 4).

B. (+)-(3aS,7aR)-Hexahydro-(3S,6R)-dimethyl-2(3H)-benzofuranone. To a 1-L round-bottomed flask equipped with an efficient magnetic stirrer is added 10 g (58 mmol) of (-)-(1R,3R,4S,8R)-p-menthane-3,9-diol and 400 mL of dichloromethane. The resulting suspension is stirred until all the solid dissolves at which time a mixture of powdered potassium permanganate and copper sulfate ($\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$) (Note 5) is added in one portion. The reaction mixture is then stirred at 25°C between 6 and 8 hr depending upon the quality of the oxidant (Note 6), 400 mL of ether is added, and stirring is continued for an additional 20 min. The suspension is transferred with the aid of a small amount of ether onto a fritted-disk Büchner funnel containing 50 g of silica gel and a little ether. The spent manganese salt is mixed with some of the silica gel, using a spatula, to insure that all the solution is absorbed. The resulting filter-cake is washed with 500 mL of ether (Note 7). Upon removal of the solvent, the crude product is obtained as a clear, colorless oil. More product is recovered by taking the filter-cake from the funnel and placing it in a 2-L beaker containing 100 mL of ether

and a solution of 270 g of sodium metabisulfite in 1 L of water that is cooled in an ice bath (Note 8). The cake is broken up with a glass rod and stirred. To the resulting slurry, 150 mL of aqueous 10% hydrochloric acid is added in portions with stirring until the color turns from dark gray to pale yellow and all the solid material, except the silica, is dissolved. The resulting mixture is filtered and the filtrate is extracted with three 150-mL portions of ether. The ether extracts are combined and washed twice with water and once with brine. The ethereal solution is dried by shaking with 30 g of anhydrous sodium sulfate and filtered. The filtrate is concentrated to about 150 mL and stirred with 10 g of Amberlyst-15 for 3 hr (Note 9). After another filtration, the solvent is evaporated and the residual oil is combined with that previously obtained. Purification by vacuum distillation gives 4.8-5.0 g (49-51% yield) of 3aS,7aR-hexahydro-3S,6R-dimethyl-2(3H)-benzofuranone as a colorless oil, bp 110°C (0.05 mm) (Note 10).

2. Notes

1. Isopulegol (Tech. as obtained from Aldrich-Chemie GmbH & Company KG, D-7924 Steinheim, Federal Republic of Germany) contains about 65-70% (-)-isopulegol according to its NMR spectrum. It has an optical rotation of $[\alpha]_D^{20} -4.6^\circ$ (neat), while $[\alpha]_D^{20} -22^\circ$ is reported² for the pure material. The technical grade product was used without further purification. Pure (-)-isopulegol can be prepared in a highly stereoselective manner from (+)-citronellal.³

2. Tetrahydrofuran (THF) was dried with and distilled from sodium in the presence of benzophenone.

3. Diborane was obtained as a 1.0 M THF solution from Aldrich Chemical Company, Inc.

4. The NMR spectrum of the diol obtained was identical to that already reported:² ¹H NMR (360 MHz, CDCl₃) δ: 0.86-0.99 (m, 2 H), 0.92 (d, 3 H, J = 6.6), 0.96 (d, 3 H, J = 7.5), 1.17-1.29 (m, 1 H), 1.32-1.49 (m, 2 H), 1.57 (m, 1 H), 1.64 (m, 1 H), 1.85 (m, 1 H), 1.96 (m, 1 H), 3.29 (br, s, 2 H), 3.47 (t, d, 1 H, J = 10.4, 4.2), 3.60 (dd, 1 H, J = 10.6, 3.5), 3.66 (dd, 1 H, J = 10.6, 5.4). Its optical rotation ($[\alpha]_{\text{D}}^{20}$ -18.7° (CHCl₃, c 10)) was identical to that reported.² The checkers recorded an $[\alpha]_{\text{D}}^{20}$ of -20.7° (CHCl₃, c 10).

5. The oxidant was prepared from 130 g of crystalline potassium permanganate (KMnO₄) and 25 g of CuSO₄·5H₂O by grinding them together in a mortar until a fine powder was obtained.

6. The progress of the oxidation can be monitored by the disappearance of the diol using TLC (eluent, hexane:ethyl acetate, 2:7).

7. It is essential to mix thoroughly the spent oxidant and the silica gel with a spatula while washing. This process does not cause any manganese salt to pass into the filtrate.

8. The quality of the KMnO₄ and CuSO₄·5H₂O varies with the supplier and affects the yield. Consequently, some hydroxy acid, instead of the lactone, may be formed. In such a case, treatment with sodium metabisulfite solution followed by acidification, converts any free acid retained on the filter cake into lactone.

9. Amberlyst-15, a cation exchange resin, was supplied by Fluka Chemical Corporation.

10. The lactone is identical to that previously reported⁴ and has the following spectral data: IR (neat) cm⁻¹: 1770, 1453, 1375, 1290, 1190, 1096, 847; ¹H NMR (360 MHz, CDCl₃) δ: 0.99-1.38 (m, 3 H), 1.02 (d, 3 H, J = 6.5), 1.15 (d, 3 H, J = 7.6), 1.59 (m, 1 H), 1.78 (m, 2 H), 1.92 (m, 1 H), 2.25 (m, 1 H), 2.64 (quint., 1 H, J = 7.6), 4.00 (dt, 1 H, J = 11, 4); ¹³C NMR (360 MHz, CDCl₃) δ: 9.57, 21.99, 23.77, 31.25, 34.15, 38.72 (2 carbons), 47.09, 81.38, 180.27. It has $[\alpha]_{\text{D}}^{20}$ +106.2° (CHCl₃, c 0.6). The checkers

recorded $[\alpha]_D^{25}$ of +72 to +88° (CHCl_3 , c 0.6). If the temperature of the distillation exceeds 110°C, a decrease in $[\alpha]_D$ might be observed because of epimerization α to the lactone carbonyl. If the pure diastereomer is required, it is recommended that purification be effected by column chromatography over silica gel (eluent, pentane:ethyl acetate 20:1). Typically, the lactone is obtained in a yield of 55% with an $[\alpha]_D^{20}$ +149° (CHCl_3 , c 1.1).

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

There are few oxidants that oxidize primary alcohols faster than secondary ones. We have demonstrated that a solid mixture of KMnO_4 and $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ treated with base can bring about such selectivity.⁴ The present procedure illustrates a general and convenient method for the oxidation of α,ω -diols to give lactones, that is typified by procedure B, where base is not necessary since ideally no acid is produced. When conducted on a 1-g scale and using pure (-)-isopulegol, overall yields were as high as 89%. In the present instance, starting with pure diol in 10-g lots, maximum yields of only 55% were attained. The reason for the lower yield on larger scale is unclear, although the formation of hydroxy acid rather than lactone may account for some loss. Nonetheless, the procedure has undeniable advantages, including, the formation of a single lactone retaining the initial stereochemistry at C(3). Although Jones oxidation of the diol⁵ is reported to give the product lactone in 89%

yield, repetition of the experiment reveals that only 38% is found in practice, the balance of material being two other related, but different products.⁴ Other routes^{6,7} to this lactone, because of the conditions, give most probably the 3R epimer as evidenced by the NMR spectral data.

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

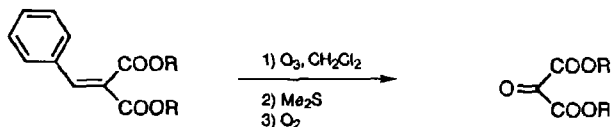
(3aS,7aR)Hexahydro-(3S,6R)-dimethyl-2(3H)-benzofuranone: 2(3H)-Benzofuranone, hexahydro-3,6-dimethyl-, [3R-(3 α ,3a β ,6 β ,7a α)]- (10); (79726-51-5)

(-)-(1R,3R,4S,8R)-p-Menthane-3,9-diol: p-Menthane-3,9-diol, (1R,3R,4S,8R)-(-)- (8,9); Cyclohexaneethanol, 2-hydroxy- β ,4-dimethyl-, [1S,-[1 α (S*),2 β ,4 β]]- (10); (13834-07-6)

Isopulegol: Cyclohexanol, 5-methyl-2-(1-methylethenyl)-, [1R-(1 α ,2 β ,5 α)]- (9); (89-79-2)

Dibroane: Furan, tetrahydro-, compd. with borane (1:1) (8,9); (14044-65-6)

**DIALKYL MESOXALATES BY OZONOLYSIS OF DIALKYL
BENZALMALONATES: PREPARATION OF DIMETHYL MESOXALATE**
(Propanedioic acid, oxo-, dimethyl ester)



Submitted by Lutz F. Tietze and Matthias Bratz.¹

Checked by Makoto Kaino and Hisashi Yamamoto.

1. Procedure

A 300-mL wash bottle with an inlet tube fitted with a wide pore glass frit and equipped with a stirring bar is charged with 40.0 g (0.18 mol) of dimethyl benzalmalonate (Note 1) dissolved in 150 mL of dichloromethane. The cooled solution (0°C, ice bath) is purged with argon (10 min) and then a stream of ozone is passed through with vigorous stirring for 4.5 hr (Note 2). After the reaction is complete (TLC, silica gel, diethyl ether/petroleum ether = 1:1), excess ozone is removed by purging with argon (10 min) and 15 mL of dimethyl sulfide (Note 3) is slowly added at 0°C (ice bath). Stirring is continued for 1 hr at this temperature and 2 hr at ambient temperature. Finally, air is blown through the solution for 12 hr (Note 4) and the residue is distilled at 20 mm, boiling range 90-100°C (Note 5) to give a yellow liquid that is further purified by filtration through 150 g of silica gel (SiO₂) (Note 6) (elution with diethyl ether). The solvent is removed under reduced pressure and the residue is recrystallized from ethyl acetate to give 23.9 g (80%) of the dimethyl mesoxalate

hydrate as colorless crystals (Note 7). Dehydration of the product is accomplished by azeotropic removal of water. The hydrate is dissolved in dichloromethane (150 mL) and heated for 12 hr in a Soxhlet apparatus (Note 8) equipped with a thimble containing layers of phosphorus pentoxide and basic alumina. The solvent is then evaporated and the residue distilled at reduced pressure to give 20.1 g (76%) of the ester as a yellow liquid [bp 94°C (20 mm)].

2. Notes

1. Dimethyl benzalmonate and the corresponding esters of other alcohols can be prepared according to an Organic Syntheses procedure or as described in standard textbooks.²

2. A Fischer Ozonizator 502 was used. The flow was adjusted to about 70 L/hr and the ozone content to 2-3 vol.%. The checkers used Japan Ozone Co. Ltd. 0-3-2 Ozonator. The flow was adjusted to about 1.3 mmol/min. Efficiency of stirring affects the yield greatly.

3. Dimethyl sulfide (Me_2S) was purchased from Tokyo Kasei; it is also available from Aldrich Chemical Company, Inc.

4. By this procedure the benzaldehyde is oxidized to benzoic acid, which is easily removed from the products.

5. Esters of higher alcohols may be filtered directly through silica gel and further purified by recrystallization.

6. Silica gel is 60 mesh.

7. All ester hydrates prepared were crystalline and can be stored without decomposition.

8. A 250-mL Soxhlet apparatus was used.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

The method described is an improved procedure based on a work appearing in the patent literature.³ Mesoxalates have been prepared by direct oxidation of malonates with selenium dioxide (SeO_2) or nitrogen dioxide (N_2O_4),⁴ by thermolysis of brominated malonates,⁵ or by oxidative cleavage of malonates with ozone⁶ or singlet oxygen.⁷ Diethyl mesoxalate is commercially available.

The procedure described has advantages over previously published methods. The starting material is easily obtained on a large scale at low cost. The ozonolysis can be conducted even on a large scale (150 g) and the workup is simple since the benzoic acid that is also formed can be removed by distillation, chromatography, or crystallization. The method is general and can be applied to different esters including chiral derivatives such as dimenthyl mesoxalate (see Table).

Mesoxalates are highly reactive substrates because of their strongly polarized carbon-oxygen bond. They have been used in pericyclic processes (e.g. Diels-Alder reactions,⁸ ene reactions,⁹ [3+2]¹⁰ and [2+2]¹¹ cycloadditions), in aldol¹² and Wittig as well as Friedel-Crafts reactions.¹³ Further applications arise from the use of the corresponding imines in hetero Diels-Alder reactions¹⁴ and electrophilic cyclizations.¹⁵

TABLE
PREPARATION OF DIALKYL MESOXALATES

Ester Hydrate			Ester
R	Yield [%]	m.p.°C (Solvent)	b.p. [°C]
Me	77	76 (ethyl ether)	110/17 mm
i-Pr	70	56-57 (t-BuOMe/pet. ether)	96/10 mm
Benzyl	86	55-57 (t-BuOMe/pet. ether)	
(-)-Menthyl	74	115 (Et ₂ O/pet. ether)	
(-)-Bornyl	42	93-95 (Et ₂ O/pet. ether)	

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

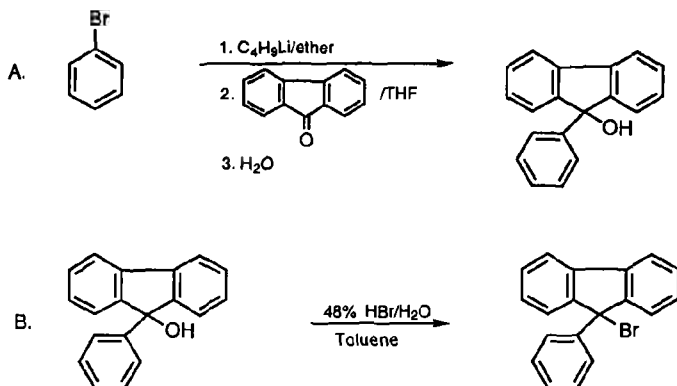
Dimethyl mesoxalate: Propanedioic acid, oxo-, dimethyl ester (9); (3298-40-6)

Dimethyl benzalmalonate: Malonic acid, benzylidene-, dimethyl ester (8);

Propanedioic acid, (phenylmethylene)-, dimethyl ester (9); (6626-84-2)

Dimethyl sulfide: Methyl sulflide (8); Methane, thiobis- (9); (75-18-3)

9-BROMO-9-PHENYLFLUORENE
(9H-Fluorene, 9-bromo-9-phenyl-)



Submitted by T. F. Jamison, W. D. Lubell, J. M. Dener, M. J. Krisché, and H. Rapoport.¹
Checked by Carol M. Taylor and Amos B. Smith, III.

1. Procedure

Caution! Butyllithium is an air-sensitive, pyrophoric material and should be kept under an inert atmosphere at all times. Persons following this procedure should be thoroughly familiar with the handling of air-sensitive solutions (Note 1). Bromobenzene is an irritant and a potential carcinogen.

A. *9-Phenyl-9-fluorenol.* A flame-dried, 3-L, three-necked, round-bottomed flask equipped with an overhead stirrer, rubber septum, and glass stopper, under a nitrogen atmosphere, is charged with bromobenzene (158 mL, 1.5 mol, Note 2) and ethyl ether (800 mL, Note 2). The solution is cooled in an ice bath and stirred at 0°C.

A flame-dried, 1-L, graduated cylinder fitted with a rubber septum is filled with 767 mL of a 1.5 M solution of butyllithium in hexane (1.15 mol, Note 3) under a nitrogen atmosphere. The butyllithium solution is then added to the 0°C ether solution over 30 min via a Teflon cannula with a positive nitrogen pressure. After the addition is complete, the solution is stirred for 20 min at 0°C and a solution of fluorenone (180 g, 1 mol, Note 4) in tetrahydrofuran (THF) (300 mL, Note 5) is added over 25 min via a Teflon cannula using positive nitrogen pressure. The ice bath is removed, the mixture is allowed to reach room temperature (24°C), and stirred for 2 hr. During this time, lithium bromide precipitates out of the reaction mixture. Water (250 mL) is added to dissolve the precipitate, the layers are separated, and the organic layer is washed with 800 mL of water and 800 mL of brine. The brine wash is discarded, and the other aqueous layers are combined and extracted with ethyl ether (2 x 200 mL). The combined organic layers are evaporated on a rotary evaporator at an initial bath temperature of 30-35°C and, when most of the volatile material has been removed, at a bath temperature of 70-75°C until a yellow solid is obtained (Note 6).

B. 9-Bromo-9-phenylfluorene. The yellow solid obtained in Step A is dissolved in toluene (800 mL, Note 7) and transferred to a three-necked, 2-L Morton flask (Note 8) equipped with an overhead stirrer, a nitrogen-filled balloon, and a glass stopper. Aqueous hydrobromic acid (HBr) (48%, 400 mL, Note 9) is added, and the heterogeneous mixture is vigorously stirred at room temperature (ca. 20-25°C) for 24 hr (Note 10). The layers are separated, the aqueous layer is extracted with toluene (400 mL), the combined organic layers are dried over sodium sulfate (Na₂SO₄) and filtered. The filter cake is washed with ethyl acetate (2 x 50 mL), and the combined organic filtrate and washings are evaporated to a yellow solid. Recrystallization from isooctane (1.25 L, Note 7) gives 270 g (84%) of 9-bromo-9-phenylfluorene (Notes 11-14).

2. Notes

1. A pamphlet describing techniques for the handling of air-sensitive solutions can be ordered from Aldrich Chemical Company, Inc.

2. Bromobenzene and ethyl ether were obtained from the Fisher Scientific Company. Bromobenzene was distilled from calcium hydride (CaH_2) under vacuum, and ethyl ether was distilled from sodium/benzophenone. Each liquid was transferred to the reaction vessel via glass syringe or Teflon cannula under a positive nitrogen pressure.

3. Butyllithium was obtained as a solution in hexane from Foote Mineral Ltd. and titrated with 0.5 M 2-propanol in tetrahydrofuran (THF) with 1,10-phenanthroline as the indicator. The butyllithium was transferred via Teflon cannula under positive nitrogen pressure. The checkers used a 1.6 M solution of butyllithium purchased from Aldrich Chemical Company, Inc.

4. Fluorenone was obtained from Chemical Dynamics Corporation or Fluka Chemical Corporation and recrystallized from absolute ethanol to remove fluorene.

5. Tetrahydrofuran was obtained from the Fisher Scientific Company and distilled from lithium aluminum hydride (LiAlH_4). (See warning: *Org. Synth., Coll. Vol. V* 1973, 976).

6. The physical properties of 9-phenyl-9-fluorenone, which was recrystallized from isooctane to give pale yellow, translucent needles, are as follows: ^{13}C NMR (Nicolet, 200 MHz) δ : 83.5, 120.0, 124.7, 125.3, 127.1, 128.1, 128.4, 129.0, 139.5, 143.1, 150.3; mp 107-108°C (lit. mp 85°C,^{3a} 107°C^{3b}). The checkers observed mp 85-86°C. Anal. Calcd for $\text{C}_{19}\text{H}_{14}\text{O}$: C, 88.34; H, 5.46. Found: C, 88.39; H, 5.60.

7. Toluene and isooctane (2,2,4-trimethylpentane) were obtained from the Fisher Scientific Company and used without further purification.

8. Use of a Morton flask and an overhead stirrer allows for better mixing of the two-phase system and gives conversion to product faster than does use of a standard round-bottomed flask with an overhead stirrer.

9. Aqueous hydrobromic acid (HBr) (48%) was obtained from the J. T. Baker Chemical Company.

10. The relative amounts of 9-phenyl-9-fluoreno1 and 9-bromo-9-phenylfluorene were determined as follows: A ^{13}C NMR spectrum (CDCl_3 solution, Bruker 400 MHz) of an authentic sample of 9-bromo-9-phenylfluorene was recorded and then doped in 1% increments with authentic 9-phenyl-9-fluoreno1. A ^{13}C NMR spectrum (CDCl_3 solution, Bruker 400 MHz) was recorded after each doping, and the heights of the peaks at 120.3 ppm (bromide) and 120.0 ppm (alcohol) were monitored. These spectra were compared with a ^{13}C NMR spectrum (CDCl_3 solution, Bruker 400 MHz) of the sample in question. Application of this technique to an evaporated aliquot of the reaction mixture in Step B, indicated >97% conversion of alcohol to bromide after 24 hr.

11. 9-Bromo-9-phenylfluorene is greater than 99% pure as shown by ^{13}C NMR, (determined by the procedure in Note 10); mp 99°C (lit.² mp 99°C).

12. The physical properties of 9-bromo-9-phenylfluorene, which was recrystallized from isooctane to give light-yellow, lustrous flakes, are as follows: ^{13}C NMR δ : 67.5, 120.3, 126.1, 127.4, 128.0, 128.3, 128.5, 129.0, 138.1, 141.1, 149.6; mp 99°C (lit.² mp 99°C); IR (CHCl_3) cm^{-1} : 3060 (m), 3000 (m), 1600 (w), 1485 (m), 1445 (s), 1150 (m), 830 (w), 690 (m), 620 (m); UV (EtOH) λ , nm, (ϵ): 310 (8,000), 276 (29,000), 238 (59,000), 230 (70,000), 213 (78,000). Anal. Calcd. for $\text{C}_{19}\text{H}_{13}\text{Br}$: C, 71.04; H, 4.08; Br, 24.88. Found: C, 71.11; H, 4.13; Br, 25.07.

13. The submitters report that 9-bromo-9-phenylfluorene of poorer quality can also be prepared on an identical scale in a lower yield using phenyllithium (obtained from Aldrich Chemical Company, Inc.) following the procedure given in Step A with

minor modifications: A black solution of phenyllithium (632 mL, 1.14 mol, Note 14) was added to a 0°C solution of fluorenone (180.2 g, 1 mol, Note 4) in THF (1360 mL, Note 5) over 30 min, and the solution was stirred for 2 hr at room temperature (24°C). Isolation as described in Step A and conversion to the bromide as described in Step B, afforded 234 g (72.8%) of 9-bromo-9-phenylfluorene as an orange/yellow solid (mp 98°C, lit.² mp 99°C); >99% pure [¹³C NMR (Note 10)] that was contaminated with approximately 20 g of a black solid; mp 91-94.5°C. This alternative procedure was not checked by the checkers.

14. Phenyllithium ("2.0 M" in cyclohexane/ether, 70/30, found to be 1.8 M by titration as described in Note 3) was obtained from the Aldrich Chemical Company, Inc., as a black solution and was added to the solution of fluorenone via Teflon cannula under positive nitrogen pressure.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

Alkylation of α -amino esters with 9-bromo-9-phenylfluorene serves as the principal step in the preparation of N-(9-phenylfluoren-9-yl)- α -amino carbonyl compounds which are useful chiral educts for asymmetric synthesis. A discussion of the synthetic utility of N-9-phenylfluoren-9-yl derivatives of amino acids and amino acid esters appears in the procedure following.

The preparation reported here is based on the method of Christie and Rapoport.⁴ 9-Bromo-9-phenylfluorene has also been prepared by a light-initiated reaction of bromine and 9-phenylfluorene in carbon disulfide,² by addition of phenylmagnesium bromide to fluorene^{3b} followed by treatment with acetyl bromide,⁵ and by treatment of 9-phenylfluorene with N-bromosuccinimide.⁶

1. Department of Chemistry, University of California, Berkeley, CA 94720.
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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

9-Bromo-9-phenylfluorene: 9H-Fluorene, 9-bromo-9-phenyl- (9); (55135-66-5)

Butyllithium, lithium, butyl- (8,9); (109-72-8)

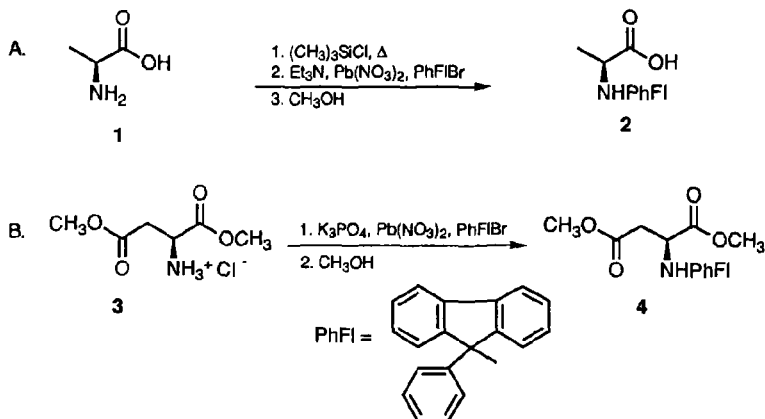
Bromobenzene, Benzene, bromo- (8,9); (108-86-1)

Hydrobromic acid (8,9); (10035-10-6)

9-Phenyl-9-fluorenol: Fluoren-9-ol, 9-phenyl- (8); 9H-Fluoren-9-ol, 9-phenyl- (9); (25603-67-2)

Fluorenone: Fluoren-9-one (8); 9H-Fluoren-9-one (9); (486-25-9)

**(S)-N-(9-PHENYLFLUOREN-9-YL)ALANINE AND
(S)-DIMETHYL N-(9-PHENYLFLUOREN-9-YL)ASPARTATE
L-Alanine, N-(9-phenyl-9H-fluoren-9-yl)- and L-Aspartic acid,
N-(9-phenyl-9H-fluoren-9-yl)-, dimethyl ester)**



Submitted by T. F. Jamison^{1a} and H. Rapoport.^{1b}

Checked by Carol M. Taylor and Amos B. Smith, III.

1. Procedure

Caution! Chlorotrimethylsilane is moisture-sensitive and should be kept under an inert atmosphere at all times. Persons following this procedure should be thoroughly familiar with the handling of moisture-sensitive materials. Lead nitrate [Pb(NO₃)₂] is toxic (†), and it and tripotassium phosphate (K₃PO₄) are hygroscopic.

A. *(S)-N-(9-Phenylfluoren-9-yl)alanine* (2).² A 1-L, flame-dried, three-necked Morton flask (Note 1) equipped with an overhead stirrer, rubber septum, and reflux condenser (equipped with a rubber septum) under a nitrogen atmosphere is charged with L-alanine (1, 13.5 g, 150 mmol, Note 2), chloroform (375 mL, Note 3), acetonitrile (75 mL, Note 4), and chlorotrimethylsilane (19.04 mL, 150 mmol, Note 5). The rubber septum in the neck of the Morton flask is replaced with a glass stopper, and the mixture is heated at reflux for 2 hr with vigorous stirring under an inert atmosphere (Note 6). The mixture is cooled to room temperature under a stream of nitrogen, triethylamine (46.0 mL, 330 mmol, Note 7) is added via syringe at a rate sufficient to maintain a gentle reflux, and the mixture is stirred for 15 min after which $\text{Pb}(\text{NO}_3)_2$ (33.1 g, 100 mmol, Note 8) is added. The glass stopper is replaced with a rubber septum, and a solution of 9-bromo-9-phenylfluorene (57.8 g, 180 mmol, Note 9) in chloroform (180 mL, Note 3) is added via a Teflon cannula with a positive nitrogen pressure. The reflux condenser is replaced with a glass stopper, and an 18-gauge syringe needle equipped with an argon-filled balloon is inserted in the rubber septum. The heterogeneous, off-white mixture is stirred vigorously under this inert atmosphere for 48 hr. After about 20 hr, the reaction mixture becomes orange and darkens over time. Methanol (15.2 mL, 375 mmol, Note 10) is then added, and the mixture is stirred an additional 30 min.

The mixture is filtered using a sintered glass filter, the filter cake is washed by stirring with chloroform (3 x 50 mL), and the dark orange filtrate is evaporated to a residue that is partitioned between ether (750 mL, Note 11) and aqueous 5% citric acid (750 mL, Note 12). The layers are separated, and the aqueous layer is extracted with ether (4 x 250 mL). The combined organic solutions are extracted with 1 M sodium hydroxide (300 mL). The aqueous solution is washed with 300 mL of ether, cooled to 0°C with stirring using a magnetic stir bar, and the pH is adjusted to 7 by the dropwise addition of glacial acetic acid (approximately 17 mL, Note 13). The mixture

now containing an off-white precipitate is extracted with 25% 2-propanol (Note 14) in chloroform (3 x 300 mL). The combined organic solutions are washed with 150 mL of saturated sodium chloride solution, dried (Na_2SO_4), filtered, and evaporated to a light yellow foam that is dried under reduced pressure to give 39.2 g (80% yield) of (S)-N-(9-phenylfluoren-9-yl)alanine (2) (Note 15).

B. (S)-Dimethyl N-(9-phenylfluoren-9-yl)aspartate (4).³ A 1-L, flame-dried, three-necked Morton flask (Note 1) equipped with an overhead stirrer and two rubber septa under a nitrogen atmosphere is charged with $\text{Pb}(\text{NO}_3)_2$ (28.2 g, 85.0 mmol, Note 8), K_3PO_4 (44.6 g, 210 mmol, Note 16), and acetonitrile (250 mL, Note 4). (S)-Dimethyl aspartate hydrochloride (3, 19.8 g, 100 mmol, Note 17) is added, followed by 9-bromo-9-phenylfluorene (40.15 g, 125 mmol, Note 9). The off-white, heterogeneous mixture is stirred vigorously for 22 hr, and to the mixture is added methanol (40.5 mL, 1.00 mol, Note 10); the mixture is stirred an additional 30 min and filtered through approximately 20 g of diatomaceous earth ("Celite") on a sintered glass funnel. The filter cake is washed by stirring with portions of chloroform until no UV chromophore can be detected in the filtrate (Note 18). Silica (60 g, Note 19) is added to the combined organic solutions, and the solvent is removed (rotary evaporator), leaving a dry powder. This powder is added to a column of silica (800 g, Note 19) and the column is eluted with 10% ethyl acetate in hexanes (Note 20) to give 9-methoxy-9-phenylfluorene (5.30 g, 19.5 mmol, Note 21) and then 9-phenyl-9-fluorenol (2.00 g, 7.7 mmol, Note 22). A 1/1 mixture of 9-phenyl-9-fluorenol and 4 is eluted next (2.13 g). After all the 9-phenyl-9-fluorenol has been eluted, the eluting solvent is changed to 25% ethyl acetate in hexanes (Note 20). The combined solutions of pure 4 are evaporated (rotary evaporator), yielding (S)-dimethyl N-(9-phenylfluoren-9-yl)aspartate (4) as a light yellow solid (36.1 g, 90 mmol, 90% yield, Note 23) after drying for 1 day at 0.1 mm. The 2.13-g mixture of 4 and 9-phenyl-9-fluorenol can be rechromatographed (100 g of silica, 10-25% ethyl acetate in hexane) to give an

additional 0.8 g (3.1 mmol) of 9-phenyl-9-fluorenone (for a total of 2.80 g, 10.8 mmol) and 1.3 g (3.2 mmol, 3.2% yield) of **4**, for a total of 37.4 g (93% yield) of **4**.

2. Notes

1. Use of a Morton flask and an overhead stirrer allows for better mixing of the heterogeneous system and gives conversion to product faster than does use of a standard round-bottomed flask with an overhead stirrer.

2. L-Alanine was purchased from Fisher Scientific company and used without further purification.

3. Chloroform was purchased from Fisher Scientific Company and distilled from phosphorus oxide (P_2O_5) immediately before use and added to the reaction mixture via syringe.

4. Acetonitrile was purchased from EM Science, distilled from calcium hydride (CaH_2) immediately before use and added to the reaction mixture via syringe.

5. Chlorotrimethylsilane was purchased from Aldrich Chemical Company, Inc., distilled from CaH_2 immediately before use, and added to the reaction mixture via syringe.

6. A syringe needle equipped with an argon-filled balloon should be inserted through the rubber septum on the reflux condenser. In addition, while the mixture is refluxing, the apparatus should be checked frequently for leaks.

7. Triethylamine was purchased from Fisher Scientific Company and distilled from barium oxide (BaO) immediately before use and added to the reaction mixture via syringe.

8. Lead nitrate (toxic!) was purchased from Fisher Scientific Company, dried in an oven at $160^\circ C$ for 4 days, and cooled in a desiccator, yielding a freely-flowing, white granular solid. The checkers dried it at $100^\circ C$ under 1.5 mm vacuum for 4 days.

9. 9-Bromo-9-phenylfluorene was prepared as described.⁴
10. Methanol was purchased from Fisher Scientific Company and used without further purification.
11. Ethyl ether was purchased from Fisher Scientific Company and used without further purification.
12. An insoluble brownish-orange polymer formed was carefully excluded from the organic extractions. Leaching of this material into the organic layer produces colored product.
13. Glacial acetic acid was purchased from Fisher Scientific Company and used without further purification. Near pH 7, much of the product precipitated, and the off-white mixture became difficult to stir. Distribution of the acetic acid was accomplished by manually swirling the flask.
14. 2-Propanol was purchased from Fisher Scientific Company and used without further purification.
15. Compound **2** thus obtained was of sufficient purity (>97%, as determined by elemental analysis) for direct use; but was contaminated by a small amount of highly colored impurities. IR cm^{-1} : 3070 (m), 3005 (m), 2905 (m), 1765 (m), 1735 (m), 1640 (m), 1590 (m), 1450 (s), 1390 (s), 1375 (s), 1355 (s), 690 (m), 605 (m). **2** can be recrystallized (1:1 EtOAc/hexane) to give a white solid,² mp 158-161°C. $[\alpha]_D^{25}$ -63.0° (EtOH, *c* 1.4); ¹H NMR δ : 1.09 (d, 3 H, *J* = 7.2), 2.70 (q, 1 H, *J* = 7.2), 7.36 (m, 11 H), 7.71 (m, 2 H); ¹³C NMR δ : 19.2, 52.9, 73.0, 120.19, 120.21, 125.5, 125.7, 125.9, 127.6, 128.2, 128.6, 129.1, 140.5, 140.6, 141.8, 145.9, 146.5, 176.5 (Four ¹³C NMR signals appear to be missing, possibly due to overlapping of signals.); TLC *R*_f 0.25 (~8:1 EtOAc/hexane); UV (EtOH) λ , nm (ϵ): 310 (9,600), 298 (5,000), 266 (14,000), 238 (23,000), 209 (47,000). Anal. Calcd for C₂₂H₁₉NO₂: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.4; H, 5.6; N, 4.2.

16. Potassium phosphate was obtained from Mallinckrodt Chemical and was dried at >500°C for > 12 hr, cooled in a desiccator, ground to a *fine powder* with a mortar and pestle, and stored in a desiccator before use. It must be weighed quickly, as it is hygroscopic.

17. (S)-Dimethyl aspartate hydrochloride was prepared as described³ and recrystallized from acetone to give a white crystalline solid (mp 114.5-115°C, lit.⁵ mp 116-117°C), which was stored in a vacuum desiccator before use.

18. Eight or nine 100-mL portions of chloroform, obtained from EM Science and used without further purification, were required.

19. Silica gel of 230-400 mesh was obtained from EM Science. The checkers used silica gel from J. T. Baker.

20. Both ethyl acetate and hexanes were obtained from Fisher Scientific Company and used without further purification.

21. The physical properties of 9-methoxy-9-phenylfluorene are as follows:⁶ mp 93-94°C (lit.⁶ mp 94-95°C), ¹H NMR δ : 2.96 (s, 3 H), 7.2-7.4 (m, 11 H), 7.7 (m, 2 H); ¹³C NMR δ : 51.3, 89.0, 119.9, 125.3, 125.5, 127.1, 128.0, 128.1, 128.9, 140.8, 143.4, 146.8; TLC (1/3 EtOAc/hexane, aluminum backed silica) R_f 0.85.

22. The properties of 9-phenyl-9-fluorene are as follows: TLC (1/3 EtOAc/hexane, aluminum backed silica) R_f 0.67; see ref. 4 for additional spectral and physical data.

23. The physical properties of (S)-dimethyl N-(9-phenylfluorene-9-yl)aspartate (4) are as follows:³ mp 58-59.5°C (sometimes 4 does not solidify); [α]_D -264° (CHCl₃, c 3.3); IR (CHCl₃) cm⁻¹: 3320 (w), 3005 (m), 2950 (m), 1740 (s), 1600 (w), 1440 (s), 1365 (m), 1340 (m), 1170 (m), 1010 (m), 1000 (m), 900 (w), 690 (m), 610 (w); UV (EtOH) λ (ε): 310 (9,600), 298 (8,700), 276 (22,100), 239 (43,700), 231 (50,700), 211 (66, 200); ¹H NMR δ : 2.35 (dd, 1 H, J = 15, 5.4), 2.52 (dd, 1 H, J = 15, 6.8), 3.01 (m, 1 H), 3.3 (br s, 1 H), 3.34 (s, 3 H), 3.65 (s, 3 H), 7.15-7.4 (m, 11 H), 7.7-7.8 (m, 2 H); ¹³C

NMR δ : 39.7, 51.5, 51.8, 52.7, 72.7, 119.7, 119.9, 125.4, 125.8, 125.9, 127.2, 127.4, 127.7, 128.2, 128.3, 139.7, 141.1, 144.4, 148.3, 148.5, 170.8, 174.6 (Note: Three ^{13}C NMR signals appear to be missing, possibly due to overlapping of signals.); TLC (1/3 EtOAc/hexane, aluminum backed silica) R_f 0.52. Anal. Calcd for $\text{C}_{25}\text{H}_{23}\text{NO}_4$: C, 74.8; H, 5.8; N, 3.5. Found: C, 74.6; H, 5.8; N, 3.4.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

Procedures A and B illustrate the two current methods for preparation of N-9-phenylfluoren-9-yl derivatives of amino acids and amino acid esters. Free carboxylate (as in alanine in Step A) or free hydroxyl (e.g., serine⁷) functions can be blocked for the duration of the reaction as trimethylsilyl (TMS) esters or ethers, respectively, by treatment with chlorotrimethylsilane and triethylamine. The TMS group(s) are then removed by methanolysis from carboxylic acids (as in Step A) and mild acidic hydrolysis from hydroxyl groups, both being accomplished during product isolation. In addition to **2**, the N-9-phenylfluoren-9-yl derivatives of serine,⁷ glutamic acid γ -methyl ester,⁸ and aspartic acid β -methyl ester^{3,9} have been prepared in this manner.

Substrates whose only reactive nucleophile is an amino group can be alkylated with 9-bromo-9-phenylfluorene using the method described in Step B. In addition to **4**, the N-9-phenylfluoren-9-yl derivatives of glutamate diesters,⁸ aziridines,¹⁰ and N-alkyl aspartate diesters^{3,11,12} have been prepared by this method.

Exclusion of moisture from the reagents and apparatus is most important, as 9-bromo-9-phenylfluorene hydrolyzes to 9-phenyl-9-fluorenol, which is unreactive toward free amines. Accordingly, all glassware, K_3PO_4 , $Pb(NO_3)_2$ (which scavenges bromide ion), and substrates must be dried thoroughly (as described above) and kept under an inert atmosphere prior to use. In addition, solvents must be distilled immediately before use and transferred to the reaction vessel under an inert atmosphere.

The methanol quench in Step B facilitates chromatographic purification by forming the known 9-methoxy-9-phenylfluorene,⁶ which is less polar than 9-phenyl-9-fluorenol, from 9-bromo-9-phenylfluorene (but not from 9-phenyl-9-fluorenol). Both 9-methoxy-9-phenylfluorene and 9-phenyl-9-fluorenol can be converted to 9-bromo-9-phenylfluorene by treatment with 48% hydrobromic acid (HBr).⁴

Both the stability¹³ and rigid steric bulk of the 9-phenylfluoren-9-yl group have increased significantly the utility of amino acids N-protected in this way as chiral educts for asymmetric synthesis. N-(9-Phenylfluoren-9-yl)- α -amino aldehydes maintain configurational stability at the α carbon during treatment with silica gel or triethylamine and on treatment with Wittig and organometallic reagents.^{2,7,14,15} N-(9-Phenylfluoren-9-yl)- α -amino ketones and esters behave similarly under these conditions, and they can also be regioselectively enolized and subsequently alkylated with a variety of electrophiles in good to excellent yield with modest to excellent diastereoselectivity, no detectable racemization, and no detectable alkylation on nitrogen or at the carbon corresponding to the α carbon of the starting amino acid.^{3,8-12,14,15} Consequently, these N-(9-phenylfluoren-9-yl)- α -amino carbonyl compounds have enabled the enantiospecific syntheses of many important compounds, including cyclosporin's unique amino acid MeBmt,¹⁵ other unusual amino acids,^{8,9} α -amino aldehydes,^{2,7,14,15} vinca alkaloids,^{3,11} (-)-vindoline,^{12,16} α -alkyl branched carboxylic acids,¹⁴ and the core nuclei of two antineoplastic agents.¹⁰

Removal of the 9-phenylfluoren-9-yl group has been accomplished by three different procedures: acidolysis with trifluoroacetic acid,^{2,8,10-12} catalytic hydrogenolysis,^{3,7,9,14,15} and dissolving metal reduction.¹⁵

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

(S)-N-(9-Phenylfluoren-9-yl)alanine: L-Alanine, N-(9-phenyl-9H-fluoren-9-yl)- (11); (105519-71-9)

(S)-Dimethyl N-(9-phenylfluoren-9-yl)aspartate: L-Aspartic acid, N-(9-phenyl-9H-fluoren-9-yl)-, dimethyl ester (12); (120230-62-8)

Chlorotrimethylsilane: Silane, chlorotrimethyl- (8,9); (75-77-4)

Lead nitrate: Nitric acid, lead (2+) salt (8,9); (10099-74-8)

Tripotassium phosphate: Phosphoric acid, tripotassium salt (8,9); (7778-53-2)

L-Alanine (8,9); (56-41-7)

9-Bromo-9-phenylfluorene: 9H-Fluorene, 9-bromo-9-phenyl (9); (55135-66-5)

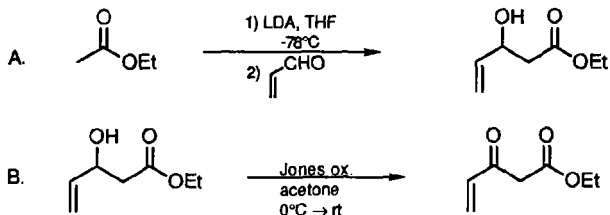
(S)-Dimethyl aspartate hydrochloride: Aspartic acid, dimethyl ester, hydrochloride, L- (8); L-Aspartic acid, dimethyl ester, hydrochloride (9); (32213-95-9)

9-Methoxy-9-phenylfluorene: 9H-Fluorene, 9-methoxy-9-phenyl- (9); (56849-87-7)

9-Phenyl-9-fluorenol: Fluoren-9-ol, 9-phenyl- (8); 9H-Fluoren-9-ol, 9-phenyl- (9); (25603-67-2)

ETHYL 3-OXO-4-PENTENOATE (NAZAROV'S REAGENT)

(4-Pentenolc acid, 3-oxo-, ethyl ester)



Submitted by R. Zibuck¹ and J. Streiber.

Checked by Michael D. Gaul and Robert K. Boeckman, Jr.

1. Procedure

Caution: Acrolein is highly toxic and a lachrymator. Handle in a well-ventilated fume hood!

A. *Ethyl 3-hydroxy-4-pentenoate.* A dry, 2-L, two-necked, round-bottomed flask, capped with septa and equipped with a thermometer (Note 1), magnetic stirring bar, and an argon inlet is flushed with argon and charged with dry tetrahydrofuran (400 mL, Note 2) and diisopropylamine (30.8 mL, 220 mmol, Note 3). The solution is cooled to -30°C and butyllithium (BuLi) (93.2 mL, 220 mmol, 2.36 M solution in hexanes, Note 4) is added. The reaction is stirred for 15 min and cooled to -76° to -78°C. Dry ethyl acetate (19.5 mL, 200 mmol, Note 5) is added dropwise so that the internal reaction temperature remains below -66°C (addition time 10-15 min). When addition of the ethyl acetate is complete, the reaction is stirred for 50 min at -70° to -78°C. A solution of freshly distilled acrolein (13.4 mL, 200 mmol, Note 6) and 100 mL of dry

tetrahydrofuran is then added rapidly via a cannula. The reaction is stirred for 5 min and quenched by the rapid addition of saturated aqueous ammonium chloride (NH_4Cl), (100 mL). The reaction mixture is poured immediately into a 2-L separatory funnel containing 500 mL of diethyl ether. The reaction flask is rinsed with 100 mL of distilled water and 100 mL of diethyl ether. After thorough mixing, the layers are separated and the aqueous layer is extracted with diethyl ether (three, 100-mL portions). The combined organic layers are washed with brine (200 mL), dried over magnesium sulfate (MgSO_4), filtered, and evaporated under reduced pressure (Note 7). Crude ethyl 3-hydroxy-4-pentenoate is used in the next step (Note 8).

B. Ethyl 3-oxo-4-pentenoate. A 1-L, round-bottomed flask equipped with a magnetic stirring bar and pressure-equalizing dropping funnel is charged with ethyl 3-hydroxy-4-pentenoate (Part A) and 400 mL of acetone. The mixture is cooled in an ice bath and Jones reagent (175 mL, Note 9) is added dropwise via the dropping funnel (addition time is approximately 30-40 min). When addition of the Jones reagent is complete, the reaction mixture is allowed to warm slowly to room temperature and is stirred overnight (10-20 hr). Methanol (20 mL) is added to quench excess Jones reagent and the reaction mixture is poured into a 2-L separatory funnel containing diethyl ether (800 mL). After thorough mixing, the layers are separated and the aqueous layer is extracted with diethyl ether (three, 200-mL portions) (Note 10). The combined organic layers are washed with brine (two, 200-mL portions), dried over MgSO_4 , filtered, and the solvent is removed by simple distillation (Note 11). Final purification is accomplished by Kugelrohr distillation (Note 12) at 0.60 mm (oven temp 45°C) with a 250-mL receiving bulb cooled to -78°C using a dry ice/isopropyl alcohol cold bath. The purified product (14.9 g, 52%) (Note 13) can be stored at -20°C for several months without decomposition.

2 Notes

1. A Fluke 51 K/J digital thermometer with temperature probe is used to monitor internal reaction temperature.

2. Tetrahydrofuran is distilled from sodium-benzophenone ketyl under argon. The reaction may be carried out using a freshly opened can of anhydrous diethyl ether from Fisher Scientific or Mallinckrodt without further purification.

3. Diisopropylamine is purified by heating to reflux over sodium hydroxide (NaOH) for 3-12 hr, followed by simple distillation from NaOH.

4. Butyllithium in hexanes (2.5 M) is purchased from Aldrich Chemical Company, Inc., and titrated using diphenylacetic acid.²

5. Ethyl acetate (500 mL) is purified by washing with 100 mL of 5% sodium carbonate solution, followed by 100 mL of saturated sodium chloride solution, drying over potassium carbonate and filtering. It is then heated at reflux over phosphorus oxide (P₂O₅) for 3-12 hr and distilled from P₂O₅.³

6. Acrolein is purchased from Aldrich Chemical Company, Inc. It is freshly distilled under reduced pressure (~20 mm) employing a dry ice/isopropyl alcohol cooled-receiver.

7. The rotary evaporator bath temperature should not exceed 40°C.

8. If desired, ethyl 3-hydroxy-4-pentenoate can be purified by Kugelrohr distillation at 0.60 mm (oven temperature 57°C) using a dry ice/isopropyl alcohol cold bath to cool the receiver (79% yield). Spectral properties are as follows: IR (film) cm⁻¹: 3437, 2984, 2938, 1732, 1373, 1275, 1030; ¹H NMR (300 MHz CDCl₃) δ: 1.22 (t, 3 H, J = 6.7, OCH₂CH₃), 2.4-2.6 (m, 2 H, C(OH)CH₂C(O)), 3.15-3.25 (br m, 1 H, OH), 4.10 (q, 2 H, J = 6.7, OCH₂CH₃), 4.44-4.57 (m, 1 H, HC(OH)), 5.05-5.35 (m, 2H), 5.78-5.90 (m, 1H); MS, m/z 145 (MH⁺).

9. Jones reagent is prepared by dissolving chromium oxide (CrO_3) (23.5 g) in concd sulfuric acid (21 mL) with cooling and then diluting with distilled water to give a total volume of 175 mL.⁴

10. Aqueous chromium waste must be bottled, labeled, and given to the waste management technical personnel.

11. The simple distillation is accomplished by using a rotary evaporator at atmospheric pressure and bath temperature $\leq 50^\circ\text{C}$. The last traces of solvent are removed under reduced pressure with an ambient temperature bath. *Caution: the product is volatile and will be lost by evaporation if care is not taken.* If water should be present, the compound can be dissolved in diethyl ether, dried again over MgSO_4 , filtered and distilled.

12. During the Kugelrohr distillation a forerun of 3-4 mL is collected and discarded.

13. The spectral properties of ethyl 3-oxo-4-pentenoate, which exists as a mixture of keto and enol forms, are: IR (film) cm^{-1} : 2984, 1741, 1659, 1588, 1423, 1242, 1150, 1038, 812; ^1H NMR (CDCl_3) δ : 1.2-1.3 (overlapping t, 3 H), 3.6 (s, ketonic H at C(2)), 4.1-4.3 (m, 2 H), 5.05 (s, enolic H at C(2)), 5.50 (app t, 1 H), 5.91-6.43 (m, 2 H), 11.8 (s, enol OH); ^{13}C NMR δ : 14.02, 14.19, 46.43, 60.23, 61.43, 91.84, 122.53, 130.16, 131.20; 135.74, 167.14, 168.61, 172.70, 192.62. Minor peaks are observed which may be the E enol form. The mass spectrum shows m/z 143 (MH^+).

Waste Disposal Information

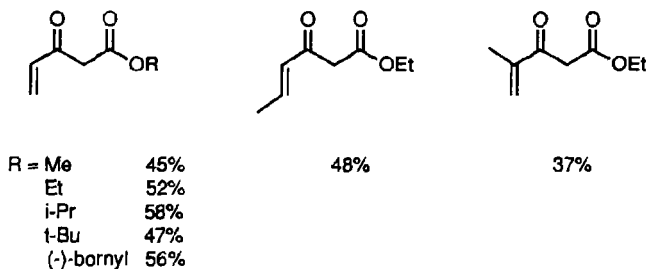
All toxic materials were disposed of in accordance with "Prudent Practices for Disposal of Chemicals from Laboratories"; National Academic Press; Washington, DC, 1983.

3. Discussion

Ethyl 3-oxo-4-pentenoate (Nazarov's reagent) is a well known annelating agent that has been used in several terpene⁵ and alkaloid⁶ syntheses.

Other preparations of Nazarov's reagent and its analogs have been reported,⁷ but many of the procedures are labor-intensive and/or require special apparatus. The reported preparation of ethyl 3-oxo-4-pentenoate is facile (2 steps) and efficient (52% overall yield). All starting materials are commercially available, relatively inexpensive, and easily purified. The synthesis is also amenable to scale up and has been carried out successfully on a 1-mol scale. Other esters have also been synthesized by this method with overall yields ranging from 45-58% (see Scheme I).⁸ Finally, methacrolein and crotonaldehyde are also suitable reactants (see Scheme I).

Scheme I



1. Wayne State University, Department of Chemistry, Detroit, MI 48202. The technical assistance of R. Keith Murphy is greatly appreciated. A portion of this work was carried out at Syracuse University, Syracuse, NY.
2. Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number);
(Registry Number)

Ethyl 3-oxo-4-pentenoate: 4-Pentenoic acid, 3-oxo-, ethyl ester (8,9);
(22418-80-0)

Ethyl 3-hydroxy-4-pentenoate: 4-Pentenoic acid, 3-hydroxy-, ethyl ester (9);
(38996-01-9)

Diisopropylamine (8); 2-Propanamine, N-(1-methylethyl)- (9); (108-18-9)

Butyllithium: Lithium, butyl- (8,9); (109-72-8)

Ethyl acetate: Acetic acid, ethyl ester (8, 9); (141-78-6)

Acrolein (8); 2-Propenal (9); (107-02-8)

Chromium(VI) oxide: Chromium oxide (8,9); Chromium oxide (8,9); (1333-82-0)

Unchecked Procedures

Accepted for checking during the period May 1, 1991
through May 1, 1992. An asterisk (*) indicates that
the procedure has been subsequently checked.

In accordance with a policy adopted by the Board of Editors, beginning with Volume 50 and further modified subsequently, procedures received by the Secretary and subsequently accepted for checking will be made available upon request to the Secretary, if the request is accompanied by a stamped, self-addressed envelope. (Most manuscripts require 54¢ postage).

Address requests to:

Professor Jeremiah P. Freeman
Organic Syntheses, Inc.
Department of Chemistry
University of Notre Dame
Notre Dame, Indiana 46556

It should be emphasized that the procedures which are being made available are unedited and have been reproduced just as they were first received from the submitters. There is no assurance that the procedures listed here will ultimately check in the form available, and some of them may be rejected for publication in *Organic Syntheses* during or after the checking process. For this reason, *Organic Syntheses* can provide no assurance whatsoever that the procedures will work as described and offers no comment as to what safety hazards may be involved. Consequently, more than usual caution should be employed in following the directions in the procedures.

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- 2563R Cyclic Hydrazines via N,N'-Diacylhydrazonium Ions: Synthesis of 1,2-Diaza-1,2-diethoxycarbonylcycloheptan-5-one.
F. P. J. T. Rutjes, H. Hiemstra, and W. N. Speckamp, Department of Organic Chemistry, University of Amsterdam, 1018 WS Amsterdam, The Netherlands
- 2580R A Simple and Convenient Method for the Oxidation of Organoboranes Using Sodium Perborate: Preparation of (+)-Isopinocampheol.
G. W. Kabalka, J. T. Maddox, T. Shoup, and K. R. Bowers, Department of Chemistry, University of Tennessee, Knoxville, TN 37996-1600
- 2594R Preparation of Bis(trimethylsilyl)peroxide (BTMSPO).
P. Dembec, A. Ricci, G. Seconi, and M. Taddei, C.N.R. - Istituto dei Composti del Carbonio contenenti Eteroatomi e loro Applicazioni, Via della Chimica, 8 40064 Ozzano Emilia (BO), Italy
- 2613R Bis-(ethylenedithio)-tetrathiafulvalene(BEDT-TTF).
T. K. Hansen, J. Becher, T. Jørgensen, K. S. Varma, R. Khedekar, and M. P. Cava, Department of Chemistry, Odense University, Campusvej 55, DK-5230, Odense M., Denmark
- 2614R A Water Soluble Tin Hydride: Tris(3-(2-methoxyethoxy)-propyl)stannane.
J. Light and R. Breslow, Department of Chemistry, Columbia University, New York, NY 10027
- 2615 Use of 1,2,4,5-Tetrabromobenzene as a 1,4-Benzadiyne Equivalent; anti- and syn-1,4,5,8-Tetrahydroanthracene-1,4:5,8-diepoxides.
K. Shahlai, S. O. Acquah and H. Hart, Department of Chemistry, Michigan State University, East Lansing, MI 48824
- 2616 Hydrogenation of Quinolines Under Water Gas Shift Conditions and Oxidation of 1,2,3,4-Tetrahydro-quinolines to Hydroxamic Acids: 6-Methoxy-1,2,3,4-tetrahydroquinoline and 1-Hydroxy-6-methoxy-3,4-dihydroquinolin-2(1H)-one.
S.-I. Murahashi, Y. Imada, and S. Watanabe, Department of Chemistry, Faculty of Engineering Science, Osaka University, Machikaneyama, Toyonaka, Osaka 560, Japan
- 2621 Chiral (Acyloxy)borane Complex Catalyzed Asymmetric Diels-Alder Reaction: (1R)-1,3,4-Trimethyl-3-cyclohexene-1-carboxaldehyde.
K. Furuta, Q.-z. Gao, and H. Yamamoto, Department of Applied Chemistry, Faculty of Engineering, Nagoya University, Furocho, Chikusa, Nagoya 464, Japan

- 2622 3,3-Difluoroallyltrimethylsilane.
J. Gonzalez, M. J. Foti, and S. Elsheimer, Department of Chemistry,
University of Central Florida, Orlando, FL 32816
- 2624 Highly Reactive Calcium for the Preparation of Organocalcium
Reagents: Preparation of 1-Adamantyl Calcium Halides and Their
Addition to Ketones.
R. D. Rieke, T.-C. Wu, and L. I. Rieke, Department of Chemistry,
University of Nebraska, Lincoln, NE 68588-0304
- 2625 (1R,5R)-(+)-Verbenone of High Optical Purity.
M. R. Sivik and L. A. Paquette, Department of Chemistry, The Ohio
State University, Columbus, OH 43210
- 2626* L-(S)-Glyceraldehyde Acetonide.
C. Hubschwerlen and J.-L. Specklin, F. Hoffmann-La Roche & Co.,
Ltd., Pharmaceutical Research Department, CH-4002 Basel,
Switzerland
- 2627* (3S,4S)-3-Amino-1-(3,4-Dimethoxybenzyl)-4-[(R)-2,2-dimethyl-1,3-
dioxolan-4-yl]-2-azetidinone.
C. Hubschwerlen and J.-L. Specklin, F. Hoffmann-La Roche & Co.,
Ltd., Pharmaceutical Research Department, CH-4002 Basel,
Switzerland
- 2628 N-tert-Butoxycarbonyl-L-serinal from D-Glucosamine Hydrochloride.
T. Henk, T. Kolter, and A. Giannis, Institut für Organische Chemie und
Biochemie der Universität Bonn, Gerhard-Domagk-Str. 1,
W-5300 Bonn 1, Germany
- 2629 Enantioselective Hydrolysis of cis-3,5-Diacetoxycyclopentene:
(1R,4S)-(+)-4-Hydroxy-2-cyclopentenyl Acetate.
D. R. Deardorff, C. Q. Windham, and C. L. Craney, Department of
Chemistry, Occidental College, Los Angeles, CA 90041
- 2630 (Bromomethyl)-lithium in the Preparation of Oxiranes: Ethyl 2-
Methyloxirane-2-propanoate.
D. S. Matteson and T. John Michnick, Department of Chemistry,
Washington State University, Pullman, WA 99164-4630
- 2631 Synthesis of Functionalized Enynes by Palladium/Copper-catalyzed
Coupling Reactions of Acetylenes with (Z)-2,3-Dibromopropenoic
Acid Ethyl Ester: (Z)-2-Bromo-5-(trimethylsilyl)-2-penten-4-ynoic Acid
Ethyl Ester.
A. G. Myers and P. S. Dragovich, Arnold and Mabel Beckman
Laboratories of Chemical Synthesis, California Institute of
Technology, Pasadena, CA 91125

- 2632 Detrifluoroacetylative Diazo Group Transfer: (E)-1-Diazo-4-phenyl-3-buten-2-one.
R. L. Danheiser, R. F. Miller, and R. G. Brisbois, Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139
- 2633 Synthesis of β -Lactones and Alkenes via Thiol Esters: (E)-2,3-Dimethyl-4-dodecene.
R. L. Danheiser, J. S. Nowick, J. H. Lee, and R. F. Miller, Department of Chemistry, Massachusetts Institute of Technology, Cambridge, MA 02139
- 2634* 1-Trifluoromethyl-1-cyclohexanol.
P. Ramaiah, R. Krishnamurti, and G. K. S. Prakash, Department of Chemistry, University of Southern California, Los Angeles, CA 90089
- 2635* 2,3-O-Isopropylidene-D-glyceraldehyde.
C. R. Schmid and J. D. Bryant, Chemical Process Research and Development, Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN 46285
- 2636* 2,2'-Bi-5,6-dihydro-1,3-dithiolo[4,5-b][1,4]-dithiinylidene (BEDT-TTF).
J. Larsen and C. Lenoir, Department of General and Organic Chemistry, H. C. Ørsted Institute, University of Copenhagen, DK-2100 Copenhagen, Denmark
- 2638 7-Methoxyphthalide.
X. Wang, S. O. de Silva, J. N. Reed, and V. Snieckus, The Guelph-Waterloo Centre for Graduate Work in Chemistry, University of Waterloo, Waterloo, Ont. N2L 3G1, Canada
- 2641* Phenylthioacetylene.
P. A. Magriotis and J. T. Brown, Department of Chemistry, West Virginia University, Morgantown, WV 26506-6045
- 2642* 1,3-Diols from Lithium β -Lithioalkoxides Generated by the Reductive Lithiation of Epoxides: 2,5-Dimethyl-2,4-hexanediol.
B. Mudryk and T. Cohen, Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260
- 2644 Rearrangement of trans-Stilbene Oxide to Diphenylacetaldehyde with Catalytic Methylaluminum Bis(4-bromo-2,6-di-tert-butylphenoxide).
T. Ooi, K. Maruoka, and H. Yamamoto, Department of Applied Chemistry, Faculty of Engineering, Nagoya University, Furocho, Chikusa, Nagoya 464, Japan

- 2645 Stereoselective Alkene Synthesis via 1-Chloro-1-[(dimethyl)-phenylsilyl]-alkanes and α -(Dimethyl)phenylsilyl Ketones.
A. G. M. Barrett, J. A. Flygare, J. M. Hill, and E. M. Wallace,
Department of Chemistry, Colorado State University,
Fort Collins, CO 80523
- 2646 4-Dodecylbenzenesulfonylazides.
I. Shinkai, Merck Sharp & Dohme, Research Laboratories, Division of
Merck & Co., Inc., P.O. Box 2000, Rahway, NJ 07065-0900
- 2649 Conversion of Amines to Phosphoesters: n-Decyl Diethylphosphate.
N. Nikolaides, I. Schipor, and B. Ganem, Department of Chemistry,
Cornell University, Ithaca, NY 14853
- 2650 3-(1S,2-Dihydroxyethyl)-1,5-dihydro-3H-2,4-benzodioxepine.
R. Oi and K. B. Sharpless, The Scripps Research Institute,
Department of Chemistry, 10666 North Torrey Pines Road,
La Jolla, CA 92037
- 2654 The Chemoselective Conversion of Carbonyl Compounds to Nitriles:
Ethyl 4-Cyanopentanoate.
R. Yoneda, S. Harusawa, and T. Kurihara, Osaka University of
Pharmaceutical Sciences, 2-10-65, Kawai, Matsubara, Osaka 580,
Japan
- 2655 Reaction of Sulfoxides with Diethylaminosulfur Trifluoride:
Preparation of Fluoromethyl Phenyl Sulfone, a Reagent for the
Synthesis of Fluoro Olefins.
J. R. McCarthy, D. P. Matthews, and J. P. Paolini, Marion Merrell Dow
Research Institute, 2110 E. Galbraith Road, Cincinnati, OH 45215
- 2656 Stereoselective Synthesis of 2,2-Disubstituted 1-Fluoro Olefins: (E)-
[[Fluoro(2-phenylcyclohexylidene)methyl]sulfonyl]benzene.
J. R. McCarthy, D. P. Matthews, and J. P. Paolini, Marion Merrell Dow
Research Institute, 2110 E. Galbraith Road, Cincinnati, OH 45215

The procedures in this text are intended for use only by persons with prior training in the field of organic chemistry. In the checking and editing of these procedures, every effort has been made to identify potentially hazardous steps and to eliminate as much as possible the handling of potentially dangerous materials; safety precautions have been inserted where appropriate. If performed with the materials and equipment specified, in careful accordance with the instructions and methods in this text, the Editors believe the procedures to be very useful tools. However, these procedures must be conducted at one's own risk. Organic Syntheses, Inc., its Editors, who act as checkers, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

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With Volume 62, the Editors of *Organic Syntheses* began a new presentation and distribution policy to shorten the time between submission and appearance of an accepted procedure. The soft cover edition of this volume is provided at no charge to the Division of Organic Chemistry of the American Chemical Society for distribution to its membership. Copies are also donated to the Perkin Division of the Royal Society of Chemistry (available to their members upon request), to the Society of Synthetic Organic Chemistry, Japan, for distribution to students, to the Polish Chemical Society, and the Gesellschaft Deutscher Chemiker. The soft cover edition is intended as the personal copy of the owner and is not for library use. A hard cover edition is published by John Wiley and Sons Inc. in the traditional format, and differs in content primarily in the inclusion of an index. The hard cover edition is intended primarily for library collections and is available for purchase through the publisher. Annual Volumes 60-64 have been incorporated into a new five-year version of the collective volumes of *Organic Syntheses* which has appeared as *Collective Volume Seven* in the traditional hard cover format. It is available for purchase from the publishers. The Editors hope that the new *Collective Volume* series, appearing twice as frequently as the previous decennial volumes, will provide a permanent and timely edition of the procedures for personal and institutional libraries. The Editors welcome comments and suggestions from users concerning new editions.

NOMENCLATURE

Both common and systematic names of compounds are used throughout this volume, depending on which the Editor-in-Chief felt was more appropriate. The *Chemical Abstracts* indexing name for each title compound, if it differs from the title name, is given as a subtitle. Systematic *Chemical Abstracts* nomenclature, used in both the 9th and 10th Collective Indexes for the title compound and a selection of other compounds mentioned in the procedure, is provided in an appendix at the end of each preparation. Registry numbers, which are useful in computer searching and identification, are also provided in these appendixes. Whenever two names are concurrently in use and one name is the correct *Chemical Abstracts* name, that name is preferred.

SUBMISSION OF PREPARATIONS

Organic Syntheses welcomes and encourages submission of experimental procedures which lead to compounds of wide interest or which illustrate important new developments in methodology. The Editorial Board will consider proposals in outline format as shown below, and will request full experimental details for those proposals which are of sufficient interest. Tear-out copies of this form may be found at the back of this volume. Submissions which are longer than three steps from commercial sources or from existing *Organic Syntheses* procedures will be accepted only in unusual circumstances.

Organic Syntheses Proposal Format

- 1) Authors
- 2) Title
- 3) Literature reference or enclose preprint if available.
- 4) Proposed sequence
- 5) Best current alternative(s)
- 6) a. Proposed scale, final product:
b. Overall yield:
c. Method of isolation and purification:
d. Purity of product (%):
e. How determined?
- 7) Any unusual apparatus or experimental technique:
- 8) Any hazards?
- 9) Source of starting material?
- 10) Utility of method or usefulness of product.

Submit to: Dr. Jeremiah P. Freeman, Secretary
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Notre Dame, IN 46556

Proposals will be evaluated in outline form, again after submission of full experimental details and discussion, and, finally by checking experimental procedures. A form that details the preparation of a complete procedure (Notice to Submitters) may be obtained from the Secretary.

Additions, corrections, and improvements to the preparations previously published are welcomed; these should be directed to the Secretary. However, checking of such improvements will only be undertaken when new methodology is involved. Substantially improved procedures have been included in the Collective Volumes in place of a previously published procedure.

ACKNOWLEDGMENT

Organic Syntheses wishes to acknowledge the contributions of Hoffmann-La Roche, Inc. and Merck & Co. to the success of this enterprise through their support, in the form of time and expenses, of members of the Boards of Directors and Editors.

DISPOSAL OF CHEMICAL WASTE

General Reference: *Prudent Practices for Disposal of Chemicals from Laboratories*, National Academy Press, Washington, D.C. 1983

Effluents from synthetic organic chemistry fall into the following categories:

1. **Gases**

- 1a. Gaseous materials either used or generated in an organic reaction.
- 1b. Solvent vapors generated in reactions swept with an inert gas and during solvent stripping operations.
- 1c. Vapors from volatile reagents, intermediates and products.

2. **Liquids**

- 2a. Waste solvents and solvent solutions of organic solids (see item 3b).
- 2b. Aqueous layers from reaction work-up containing volatile organic solvents.
- 2c. Aqueous waste containing non-volatile organic materials.
- 2d. Aqueous waste containing inorganic materials.

3. **Solids**

- 3a. Metal salts and other inorganic materials.
- 3b. Organic residues (tars) and other unwanted organic materials.
- 3c. Used silica gel, charcoal, filter aids, spent catalysts and the like.

The operation of industrial scale synthetic organic chemistry in an environmentally acceptable manner* requires that all these effluent categories be dealt with properly. In small scale operations in a research or academic setting, provision should be made for dealing with the more environmentally offensive categories.

*An environmentally acceptable manner may be defined as being both in compliance with all relevant state and federal environmental regulations *and* in accord with the common sense and good judgement of an environmentally aware professional.

- 1a. Gaseous materials that are toxic or noxious, e.g., halogens, hydrogen halides, hydrogen sulfide, ammonia, hydrogen cyanide, phosphine, nitrogen oxides, metal carbonyls, and the like.
- 1c. Vapors from noxious volatile organic compounds, e.g., mercaptans, sulfides, volatile amines, acrolein, acrylates, and the like.
- 2a. All waste solvents and solvent solutions of organic waste.
- 2c. Aqueous waste containing dissolved organic material known to be toxic.
- 2d. Aqueous waste containing dissolved inorganic material known to be toxic, particularly compounds of metals such as arsenic, beryllium, chromium, lead, manganese, mercury, nickel, and selenium.
3. All types of solid chemical waste.

Statutory procedures for waste and effluent management take precedence over any other methods. However, for operations in which compliance with statutory regulations is exempt or inapplicable because of scale or other circumstances, the following suggestions may be helpful.

Gases:

Noxious gases and vapors from volatile compounds are best dealt with at the point of generation by "scrubbing" the effluent gas. The gas being swept from a reaction set-up is led through tubing to a (large!) trap to prevent suck-back and on into a sintered glass gas dispersion tube immersed in the scrubbing fluid. A bleach container can be conveniently used as a vessel for the scrubbing fluid. The nature of the effluent determines which of four common fluids should be used: dilute sulfuric acid, dilute alkali or sodium carbonate solution, laundry bleach when an oxidizing scrubber is needed, and sodium thiosulfate solution or diluted alkaline sodium borohydride when a reducing scrubber is needed. Ice should be added if an exotherm is anticipated.

Larger scale operations may require the use of a pH meter or starch/iodide test paper to ensure that the scrubbing capacity is not being exceeded.

When the operation is complete, the contents of the scrubber can be poured down the laboratory sink with a large excess (10-100 volumes) of water. If the solution is a large volume of dilute acid or base, it should be neutralized before being poured down the sink.

Liquids:

Every laboratory should be equipped with a waste solvent container in which *all* waste organic solvents and solutions are collected. The contents of these containers should be periodically transferred to properly labeled waste solvent drums and arrangements made for contracted disposal in a regulated and licensed incineration facility.**

Aqueous waste containing dissolved toxic organic material should be decomposed *in situ*, when feasible, by adding acid, base, oxidant, or reductant. Otherwise, the material should be concentrated to a minimum volume and added to the contents of a waste solvent drum.

Aqueous waste containing dissolved toxic inorganic material should be evaporated to dryness and the residue handled as a solid chemical waste.

Solids:

Soluble organic solid waste can usually be transferred into a waste solvent drum, provided near-term incineration of the contents is assured.

Inorganic solid wastes, particularly those containing toxic metals and toxic metal compounds, used Raney nickel, manganese dioxide, etc. should be placed in glass bottles or lined fiber drums, sealed, properly labeled, and arrangements made for disposal in a secure landfill.** Used mercury is particularly pernicious and small amounts should first be amalgamated with zinc or combined with excess sulfur to solidify the material.

Other types of solid laboratory waste including used silica gel and charcoal should also be packed, labeled, and sent for disposal in a secure landfill.

Special Note:

Since local ordinances may vary widely from one locale to another, one should always check with appropriate authorities. Also, professional disposal services differ in their requirements for segregating and packaging waste.

** If arrangements for incineration of waste solvent and disposal of solid chemical waste by licensed contract disposal services are not in place, a list of providers of such services should be available from a state or local office of environmental protection.

PREFACE

Annual Volume 71 contains 30 checked and edited experimental procedures that illustrate important new synthetic methods or describe the preparation of particularly useful chemicals. This compilation begins with procedures exemplifying three important methods for preparing enantiomerically pure substances by asymmetric catalysis. The preparation of **(R)-(-)-METHYL 3-HYDROXYBUTANOATE** details the convenient preparation of a BINAP-ruthenium catalyst that is broadly useful for the asymmetric reduction of β -ketoesters. Catalysis of the carbonyl ene reaction by a chiral Lewis acid, in this case a binaphthol-derived titanium catalyst, is illustrated in the preparation of **METHYL (2R)-2-HYDROXY-4-PHENYL-4-PENTENOATE**. The enantiomerically pure diamines, **(1R,2R)-(+)- AND (1S,2S)-(-)-1,2-DIPHENYL-1,2-ETHYLENEDIAMINE**, are useful for a variety of asymmetric transformations: hydrogenations, Michael additions, osmylations, epoxidations, allylations, aldol condensations and Diels-Alder reactions. Promotion of the Diels-Alder reaction with a diaminoalane derived from the **(S,S)-diamine** is demonstrated in the synthesis of **(1S,endo)-3-(BICYCLO[2.2.1]HEPT-5-EN-2-YL-CARBONYL)-2-OXAZOLIDINONE**.

The preparation of enantiomerically pure chemicals is also the theme of the next group of four procedures. The biopolymer polyhydroxybutyric acid, which is now produced on an industrial scale, serves as the starting material for the large scale synthesis of **(R)-3-HYDROXYBUTANOIC ACID** and **(R)-METHYL 3-HYDROXY-BUTANOATE**. Esters of **(-)-camphanic acid** are useful derivatives for resolving and determining the enantiomeric purity of primary and secondary alcohols. An optimized preparation of **(-)-(1S,4R)-CAMPHANOYL CHLORIDE** is provided. The preparation of enantiomerically pure α -hydroxyketones from ethyl lactate is illustrated in the synthesis of **(3)-(S)-[(1*tert*)-BUTYL-DIPHENYLSILYL]OXY]-2-BUTANONE**. One use of this chiral α -hydroxyketone is provided in the synthesis of **(2S,3S)-3-ACETYL-8-**

CARBOETHOXY-2,3-DIMETHYL-1-OXA-8-AZASPIRO[4.5]DECANE, a procedure that exemplifies a new stereocontrolled method for constructing substituted tetrahydrofurans.

The vital role played by organometallic reagents in contemporary preparative organic chemistry is further demonstrated by the next cluster of 11 procedures. The preparation of **1-ACETOXY-2-BUTYL-4-METHOXYNAPHTHALENE** illustrates a versatile, regiocontrolled synthesis of 2-substituted naphthalenediol derivatives using chromium carbene complexes. **CHLOROBIS(η⁵-CYCLOPENTADIEN-1-YL)HYDRIDOZIRCONIUM (SCHWARTZ'S REAGENT)** is widely employed to access organozirconium intermediates by hydrosilylation. A convenient procedure for preparing this reagent in high purity on a large scale is provided. The companion preparation of **3-(1-OCTEN-1-YL)CYCLOPENTANONE** details a reliable zirconium-based procedure for the coupling of alkynes and enones. The immense importance of palladium catalyzed cross-coupling procedures stems to a considerable extent from the broad functional group tolerance of palladium-catalyzed reactions. The compatibility of sulfide and nitro functional groups is exemplified in the next two procedures describing the preparation of **4-(3-CYCLOHEXYL)-2-PHENYLTHIO-1-BUTENE** and **4-METHOXY-4'-NITROBIPHENYL**. An alternate regiocontrolled route to unsymmetrical biphenyls is presented in the preparation of **2,2'-DIMETHOXY-6-FORMYLBIPIHENYL**, a procedure that illustrates the unusual use of an oxazoline in aromatic substitution. The next two procedures describe the preparation of **TRIBUTYL(3-METHYL-2-BUTENYL)TIN** and the use of this allylating reagent to introduce the isoprenyl side chain of **UBIQUINONE-1**. Another application of organotin intermediates is provided in the preparation of **TRIBUTYL[(METHOXYMETHOXY)METHYL]STANNANE**, a useful hydroxymethyl anion equivalent. The accompanying procedure illustrates this use in the preparation of **1-(HYDROXYMETHYL)CYCLOHEPTANOL**. The final procedure of this group, the preparation of **ETHYL 1-NAPHTHYLACETATE**, exemplifies a one-pot ester

homologation method that proceeds by way of ynoate anion intermediates. For many esters this procedure will be a safer alternative to classical Arndt-Eistert homologation.

The next eight procedures illustrate additional important synthetic methods. The preparation of **3,4-CYCLODODECENO-1-METHYLBENZENE** demonstrates a useful procedure for benzoannulation of ketones, while the preparation of **DIMETHYL (1'R,2'R,5'R)-2-(2'-ISOPROPENYL-5'-METHYLCYCLOHEX-1'-YL)-PROPANE-1,3-DIOATE** illustrates a Knoevenagel-intramolecular ene route to *trans*-1,2-disubstituted cyclohexanes. An optimized preparation of **2-METHYLENE-1,3-DITHIOLANE** is followed by the use of this ketene thioacetal in an inverse electron-demand Diels-Alder reaction to prepare **9-DITHIOLANOBICYCLO[3.2.2]NON-6-EN-2-ONE**. The four electron component of this cycloaddition is tropone and an optimized procedure for preparing this versatile starting material on large scale by selenium dioxide oxidation of cycloheptatriene is also detailed. A method for methoxycarbonylmethylation of aldehydes is illustrated next in the preparation of **METHYL 3,3-DIMETHYL-4-OXOBUTANOATE**. The addition of a dienoxysilane to an electrophilic glycinate is the key step in a short synthesis of **4-KETOPIPECOLIC ACID**. The final procedure in this group describes the preparation of **(3aS,7aR)-HEXAHYDRO-(3S,6R)-DIMETHYL-2(3H)-BENZOFURANONE** and illustrates the use of a heterogeneous oxidant for the selective oxidation of primary alcohols.

The volume concludes with the preparation of four useful starting materials. The highly electrophilic tricarbonyl reagent **DIMETHYL MESOXALATE** finds application as a two-electron component in various pericyclic processes. **9-BROMO-9-PHENYL-FLUORENE** is becoming increasingly used for the protection of primary amines, particularly amino acids and amino esters. Two methods for introducing the 9-phenylfluorenyl group are illustrated in the preparations of **(S)-N-(9-PHENYLFLUOREN-9-YL)ALANINE** AND **(S)-DIMETHYL N-(9-PHENYLFLUOREN-9-YL)ASPARTATE**.

The final procedure in the volume documents a convenient synthesis of the classical annulating reagent **ETHYL 3-OXO-4-PENTENOATE (NAZAROV'S REAGENT)**.

The long-standing success of this series derives from the efforts of many people. I am particularly grateful to my colleagues on the Editorial Board who have contributed their insight and energies to the selection and checking of the procedures recorded in this volume. Deserving of special praise are the coworkers of the Editorial Board members who carefully checked, and in some cases modified and improved, the procedures appearing in this volume. Finally, I wish to acknowledge the invaluable contributions of Professor Jeremiah P. Freeman, Secretary to the Board and our Assistant Editor, Dr. Theodora W. Greene.

Irvine, California

Larry E. Overman

July 1992

RICHARD S. SCHREIBER

October 15, 1909 - March 7, 1992

Richard S. Schreiber, Editor of Volume 31 of *Organic Syntheses* and a long-time member of its Board of Directors, died on March 7, 1992, after a long illness.

Raised in Blue Island, Illinois, Schreiber graduated from Wabash College in 1931. He received a Ph.D. in organic chemistry from the University of Illinois in 1935, with Ralph Shriner as his adviser. He then joined the Central Research Department of the DuPont Company in Wilmington, Delaware, where he soon became leader of a research group.

Schreiber was one of the first people I met when I joined DuPont, and I was at once impressed by his cordiality, energy, and intelligence. He had a knack for exciting people about what they were doing, as I observed both in the laboratory and in the

local ACS Section one year when he chaired it and spurred it into worthwhile new activities. His DuPont coworkers were sorry to see him leave to join the Upjohn Pharmaceutical Company in 1949.

At Upjohn he became Vice President for Research and a member of the Board of Directors. Shortly after arrival he was told to pick one major area of research for Upjohn and then to do what was necessary to put Upjohn research in the front ranks of pharmaceutical research. He picked steroids as the area to emphasize, and under his direction Upjohn became a major factor in steroidal drugs and a leader in research. His friends at DuPont were not surprised to hear by the grapevine that Schreiber seemed to know all the Upjohn research people by their first names, was a stimulating leader, and answered his own phone.

In 1947, while at DuPont, he became an Editor of *Organic Syntheses*. As indicated he was Editor-in-Chief of Volume 31 in 1951. Even after his term as Editor had expired, he was willing to check preps requiring equipment not widely available. From 1955 to 1989 Schreiber was a member of the *Organic Syntheses* Board of Directors, serving as treasurer from 1967 to 1973. As a member of the *Organic Syntheses* Board, he was particularly valuable during discussions of how to invest the organization's capital, when he would preach the virtues of prudence in a clear, persuasive way.

Schreiber was active in educational matters during much of his life. Thus at various times he was on the School Board of his Wilmington district, the Board of Directors of both Kalamazoo College and Wabash College, and the Michigan Commission for Educational Policies. Among other important posts, he served on the National Advisory Cancer Council and the Michigan Science Advisory Board.

April 6, 1992

Blaine McKusick

JOHN CLARK SHEEHAN

September 23, 1915 - March 21, 1992

John C. Sheehan will long be remembered for having solved one of the most formidable and prominent problems in synthetic chemistry of the twentieth century, the chemical synthesis of the penicillins, and for helping to lead organic chemistry to new heights in the post World War II era. He made major contributions to his academic home for four decades, the Massachusetts Institute of Technology, through his teaching and research, which were instrumental in rejuvenating chemistry and maintaining its excellence at the Institute, and through the enormous financial returns from his successful work on synthetic penicillins. His fundamental research provided the chemical base for the development of modern semisynthetic penicillins which have saved countless human lives. John Sheehan played an active role in the *Organic*

Syntheses organization, having served as editor-in-chief of volume 38, as a member of the Advisory Board and Board of Directors for many years, and as an astute advisor. His was a multifaceted career shaped by his famed mentor the late Werner E. Bachmann, secret research projects during World War II on the production of explosives and antibiotics, the postwar rebuilding of Chemistry at M.I.T. under the late Arthur C. Cope, service on governmental scientific advisory committees, and leadership of private research institutes in the Boston area. His achievements demonstrated an ability to focus on chemical problems of great practical importance, the courage to pioneer against strong odds, and an unflagging determination to succeed.

John Sheehan was born and raised in Battle Creek, Michigan and was educated at local schools and at Battle Creek College. He received the Ph.D. degree in 1941 from the University of Michigan for studies in the laboratory of Werner E. Bachmann, then engaged in the historic first total syntheses of the steroid hormones equilenin and estrone. John was a superbly trained experimentalist in the grand tradition of Bachmann and Bachmann's illustrious teacher Moses Gomberg, the founder of the field of carbon free radicals. John assumed a postdoctoral position in the Bachmann laboratory with the entry of the U.S. into World War II, and, in collaboration with Bachmann, developed the large-scale method for the production of the important explosive RDX which was used by the U.S. for the remainder of the War with great success. From 1941-1946 he was a research chemist at Merck and Co. under the late Max Tishler and participated in several key projects including the program of research on penicillins.

At the invitation of Arthur C. Cope, John joined the Faculty of M.I.T. as an Assistant Professor in 1946. Cope had just been appointed as Head of the Department of Chemistry by the President of M.I.T., Karl T. Compton, on the advice of his friend and wartime associate Roger Adams of the University of Illinois. At the same

time John D. Roberts and C. Gardner Swain were brought on board by Cope, and in the next few years that foursome and their colleagues propelled M.I.T. into the front rank of U.S. chemistry. Within a period of just four years John Sheehan established himself as one of the most creative and dynamic synthetic organic chemists in the world by his discovery of new methods of synthesis of peptides (carbodiimide coupling and phthaloyl N-protection), three new syntheses of β -lactams, the first synthesis of the penicillin ring system, and the isolation and identification of a number of important new natural products.

His research on penicillins, initiated in 1948, was remarkable for several reasons. It came on the heels of the large wartime U.S.-British project of research on penicillins (involving more than one thousand chemists), which failed to develop a chemical synthesis and produced instead an ominous summary of a great many attempts. By 1948 penicillin G was produced in abundance commercially by fermentation and no other leading chemist saw any reason to take on the apparently hopeless task of synthesizing such an unstable molecule. In John's own colorful language the chemical synthesis of penicillin was like "placing an anvil on top of a house of cards." Years of determined and skillful effort were rewarded by success in 1957 when John and his group completed the first synthesis of penicillin V and also 6-aminopenicillanic acid, a key intermediate for the synthesis of a large number of superpenicillins. John later told the story of his work on penicillins in the book *"The Enchanted Ring-The Untold Story of Penicillin"* which includes an account of the complex legal skirmish over the Sheehan-MIT patents on penicillin synthesis.

John Sheehan's major research achievements are described in some 150 synthetic papers which cover not only penicillin, but peptides, antibiotics, alkaloids and steroids. For these scientific contributions John received several high honors including the American Chemical Society award in Pure Chemistry (1951), the American Chemical Society award for Creative Work in Synthetic Organic Chemistry

(1959), the John Scott Award for inventors benefiting mankind (1964), the Outstanding Achievement Award of the University of Michigan (1971), and a number of honorary doctorates.

As a graduate student in John's research group I was struck by his ingrained cheerfulness, optimism and humor, as well as his broad chemical expertise. That 1948-1950 group, which included Gerald D. Laubach (later President of Pfizer Inc), Robert T. O'Neill (later a successful research chemist at Merck and private businessman), Barry M. Bloom (President of Pfizer Research), Ajay K. Bose (Professor at Stevens Institute of Technology), and David Johnson (research director at Bristol Myers), no collection of shrinking violets, found as much enjoyment in give and take with John as in the research adventure itself.

John Sheehan was a man who made friends easily and had many close friends, including not a few in the *Organic Syntheses* family. He was an avid tennis player and boater, a close follower of politics and sports, a lover of good stories, and an entertaining dinner companion. John is survived by his lovely and devoted wife of more than fifty years, the former Marion M. Jennings; a brother, David Sheehan of Battle Creek, Michigan; three children, John C. Jr. of Denver, Colorado; David E. of Key Biscayne, and Elizabeth (Betsy) S. Watkins of Saunderstown, Rhode Island, and six grandchildren.

June 29, 1992

E. J. Corey

CONTENTS

Masato Kitamura, Makoto Tokunaga, Takeshi Ohkuma, and Ryoji Noyori	1	ASYMMETRIC HYDROGENATION OF 3-OXO CARBOXYLATES USING BINAP- RUTHENIUM COMPLEXES: (R)-(-)- METHYL 3-HYDROXYBUTANOATE
Koichi Mikami, Masahiro Terada, Satoshi Narisawa, and Takeshi Nakai	14	ASYMMETRIC CATALYTIC GLYOXYLATE-ENE REACTION: METHYL (2R)-2-HYDROXY-4- PHENYL-4-PENTENOATE
S. Pikul and E. J. Corey	22	(1R,2R)-(+)- AND (1S,2S)-(-)-1,2- DIPHENYL-1,2-ETHYLENEDIAMINE
S. Pikul and E. J. Corey	30	ENANTIOSELECTIVE, CATALYTIC DIELS-ALDER REACTION: (1S-endo)-3-(BICYCLO[2.2.1]HEPT- 5-EN-2-YLCARBONYL)-2-OXA- ZOLIDINONE
Dieter Seebach, Albert K. Beck, Richard Breitschuh, and Kurt Job	39	DIRECT DEGRADATION OF THE BIOPOLYMER POLY[(R)-3-HYDROXY- BUTYRIC ACID] TO (R)-3-HYDROXY- BUTANOIC ACID AND ITS METHYL ESTER
Hans Gerlach, Dag Kappes, Robert K. Boeckman, Jr., and Graham N. Maw	48	(-)-(1S,4R)-CAMPHANOYL CHLORIDE
Larry E. Overman and Gilbert M. Rishton	56	3-(S)-{[(tert-BUTYLDIPHENYLSILYL)- OXY]-2-BUTANONE
Larry E. Overman and Gilbert M. Rishton	63	STEREOCONTROLLED PREPARATION OF 3-ACYLTETRAHYDROFURANS FROM ACID-PROMOTED REARRANGEMENTS OF ALLYLIC KETALS: (2S,3S)-3-ACETYL- 8-CARBOETHOXY-2,3-DIMETHYL-1-OXA- 8-AZASPIRO[4.5]DECANE
Joseph M. Timko and Ayako Yamashita	72	SYNTHESIS OF 2-SUBSTITUTED NAPHTHALENEDIOL DERIVATIVES USING CHROMIUM CARBENE COMPLEXES: 1-ACETOXY-2-BUTYL- 4-METHOXYNAPHTHALENE

Stephen L. Buchwald, Susan J. LaMaire, Ralph B. Nielsen, Brett T. Watson, and Susan M. King	77	SCHWARTZ'S REAGENT
Ruen Chu Sun, Masami Okabe, David L. Coffen, and Jeffrey Schwartz	83	CONJUGATE ADDITION OF A VINYLZIRCONIUM REAGENT: 3-(1-OCTEN-1-YL)CYCLOPENTANONE
Tatsuo Ishiyama, Norio Miyaura, and Akira Suzuki	89	PALLADIUM(0)-CATALYZED REACTION OF 9-ALKYL-9-BORABICYCLO[3.3.1]- NONANE WITH 1-BROMO-1-PHENYL- THIOETHENE: 4-(3-CYCLOHEXYL)- 2-PHENYLTHIO-1-BUTENE
J. K. Stille, Antonio M. Echavarren, Robert M. Williams, and James A. Hendrix	97	4-METHOXY-4'-NITROBIPHENYL
Albert I. Meyers and Mark E. Flanagan	107	2,2'-DIMETHOXY-6-FORMYLBIPHENYL
Yoshinori Naruta, Yutaka Nishigaichi, and Kazuhiro Maruyama	118	TRIBUTYL(3-METHYL-2-BUTENYL)TIN
Yoshinori Naruta and Kazuhiro Maruyama	125	UBIQUINONE-1
Rick L. Danheiser, Karen R. Romines, Hiroo Koyama, Stephen K. GeeCarl R. Johnson, and John R. Medich	133	A HYDROXYMETHYL ANION EQUIVALENT: TRIBUTYL[(METHOXY- METHOXY)METHYL]STANNANE
Carl R. Johnson, John R. Medich, Rick L. Danheiser, Karen R. Romines, Hiroo Koyama, and Stephen K. Gee	140	PREPARATION AND USE OF (METH- OXYMETHOXY)METHYLLITHIUM: 1- HYDROXYMETHYL)CYCLOHEPTANOL
Rajaratnam E. Reddy and Conrad J. Kowalski	146	ETHYL 1-NAPHTHYLACETATE: ESTER HOMOLOGATION VIA YNOLATE ANIONS
Marcus A. Tius and G. S. Kamali Kannangara	158	BENZOANNELATION OF KETONES: 3,4-CYCLODODECENO-1-METHYL- BENZENE

L. F. Tietze and U. Beifuss	167	DIASTEREOSELECTIVE FORMATION OF TRANS-1,2-DISUBSTITUTED CYCLO-HEXANES FROM ALKYLIDENEMALONATES BY AN INTRAMOLECULAR ENE REACTION: DIMETHYL (1'R,2'R,5'R)-2-(2'-ISOPROPENYL-5'-METHYLCYCLOHEX-1'-YL)-PROPANE-1,3-DIOATE
Karl R. Dahnke and Leo A. Paquette	175	2-METHYLENE-1,3-DITHIOLANE
Karl R. Dahnke and Leo A. Paquette	181	INVERSE ELECTRON-DEMAND DIELS-ALDER CYCLOADDITION OF A KETENE DITHIOACETAL. COPPER HYDRIDE-PROMOTED REDUCTION OF A CONJUGATED ENONE. 9-DITHIOLANO- BICYCLO[3.2.2]NON-6-EN-2-ONE FROM TROPONE
Hans-Ulrich Reissig, Ingrid Reichelt, and Thomas Kunz	189	METHOXYCARBONYLMETHYLATION OF ALDEHYDES VIA SILOXYCYCLO- PROPANES: METHYL 3,3-DIMETHYL- 4-OXOBUTANOATE
Clarisse Mühlemann, Peter Hartmann, and Jean-Pierre Obrecht	200	TITANIUM-MEDIATED ADDITION OF SILYL DIENOL ETHERS TO ELECTROPHILIC GLYCINE: A SHORT SYNTHESIS OF 4-KETOPIPECOLIC ACID HYDROCHLORIDE
Charles W. Jefford, Yun Li, and Ying Wang	207	A SELECTIVE, HETEROGENEOUS OXIDATION USING A MIXTURE OF POTASSIUM PERMANGANATE AND CUPRIC SULFATE: (3aS,7aR)- HEXAHYDRO-(3S,6R)-DIMETHYL- 2(3H)-BENZOFURANONE
Lutz F. Tietze and Matthias Bratz	214	DIALKYL MESOXALATES BY OZONOLYSIS OF DIALKYL BENZALMALONATES: PREPARATION OF DIMETHYL MESOXALATE
T. F. Jamison, W. D. Lubell, J. M. Dener, M. J. Krisché, and H. Rapoport	220	9-BROMO-9-PHENYLFLUORENE
T. F. Jamison and H. Rapoport	226	(S)-N-(9-PHENYLFLUOREN-9-YL)- ALANINE AND (S)-DIMETHYL N-(9-PHENYLFLUOREN-9-YL)- ASPARTATE

R. Zibuck and J. Streiber

236 ETHYL 3-OXO-4-PENTENOATE
(NAZAROV'S REAGENT)

Unchecked Procedures

243

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